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PROCEEDINGS

OF THE

SOCIETY FOR

EXPERIMENTAL BIOLOGY AND MEDICINE

VOLUME IV

1906–1907

EDITED BY THE SECRETARY

NEW YORK

AUGUST 1, 1907

16-71814-Dec. 1

PRESS OF
THE NEW ERA PRINTING COMPANY
LANCASTER, PA.

PREFACE.

With this volume the Society inaugurated a plan of issuing *in sections* the volumes of its proceedings. The reasons for this departure are given on page 175.

The *front* covers of the seven numbers comprising this volume may be bound in the volume, if it is desired to mark off conveniently the communications of each meeting and to provide separate tables of contents. The printed matter on the rear covers of the numbers is given in the executive proceedings (page 175) or in the list printed on page 183.

The numerals in parenthesis above the titles of the abstracts (pages 1–162) indicate numerical positions in the entire series of communications presented before the Society since its organization in 1903. The numerals in the index at the end of this volume correspond with those in parenthesis above the titles of the abstracts. Consequently none of the numerals in the index of this volume duplicates any of the numerals in the indices of the first three volumes. Convenience in reference was sought by the adoption of this plan of enumeration.

The recapitulation of the names of the authors and of the titles of the communications, presented on page 163, serves as an "author index." Only the numerals in parenthesis above the abstracts are given in it.

The constitution and by-laws, as reprinted on pages 185–8, include all amendments.

NEW YORK,
August 1, 1907.

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SCIENTIFIC PROCEEDINGS.

ABSTRACTS OF THE COMMUNICATIONS.

Eighteenth meeting.

Cornell University Medical College, New York City. October 17, 1906. President Flexner in the chair.

1 (144)

The formation of glycogen from sugars by muscle, with a demonstration of a perfusion apparatus.

By **R. A. HATCHER** and **C. G. L. WOLF.**

[*From the Chemical and Pharmacological Laboratories of the Cornell University Medical College, New York City.*]

Contrary to the findings of Külz, saccharose does not form glycogen in muscle. Glucose is a direct glycogen former in muscle. When the glycogen-free muscles of animals which have been starved and treated with strychnin are used, no glycogen is formed either by glucose or saccharose.

A perfusion apparatus was shown which permits the simultaneous and separate perfusion of the hind limbs of an animal and the arterialization of the blood by the lungs of two animals, each pair of lungs being used for an individual limb.

2 (145)

Bile media in typhoid diagnosis.

By **B. H. BUXTON.**

[*From the Department of Experimental Pathology, Loomis Laboratory, Cornell University Medical College, New York City.*]

Ten c.c. of blood are drawn from a vein and distributed into three flasks of sterilized ox bile, 20 c.c. of bile in each flask.

Of twenty seven cases of suspected typhoid examined in the

course of two months, seven were reported negative and twenty positive. Of the seven negative cases, six proved to be certainly not typhoid, and one was very doubtful. Excluding the doubtful case, there is a record of 100 per cent. in cases ranging from the fifth to the nineteenth day. By means of litmus-lactose-agar plates, reports can be made in 24 hours with a fair degree of certainty. After incubating the bile-blood over night, streaks are drawn over the plates, and in 5 or 6 hours a growth may be visible. If the growth prove to be a bacillus which reacts to a microscopical Widal test the case is reported positive.

3 (146)

The inconstant action of muscles.

By **WARREN P. LOMBARD** and **F. M. ABBOTT**.

[*From the Physiological Laboratory of the University of Michigan.*]

The movements of the hind leg of the frog which are generally ascribed to finely adjusted nervous coördination, are in fact largely the result of the mechanical conditions under which the muscles act. These conditions differ with each new position of the bones entering into the joints of the limb, and consequently alter the effects of the contractions of muscles as the positions of the bones change during the course of any given movement. Thus a muscle which in one position of a bone may act as a flexor, in another position may act as an extensor, and a muscle which in one position of a bone may carry it dorsally, in another position may carry it ventrally. Manifestly it is absurd to try to class muscles as flexors and extensors, for example, or to try to name them according to the movement which they are supposed to produce. Nor can one, without qualification, speak of certain muscles as antagonists, when under slightly modified conditions of action they act as synergists. Moreover, it is evident that we can form no estimate of the part played by the central nervous system in coördinated movements of locomotion, for example, until we have ascertained in how far the coördination observed is due to the mechanical conditions under which the muscles are acting. A study of central coördination must, in short, be postponed until

the effects of peripheral coördination based on joint and muscle mechanics has been ascertained. These statements are the result of two years of careful study of the effect of mechanical conditions on the action of the separate muscles of the hind leg of the frog, when these muscles have been electrically excited to action, in different positions of the bones.

4 (147)

The senses and intelligence of the Chinese dancing mouse.

By **ROBERT M. YERKES.**

[*From the Psychological Laboratory of Harvard University.*]

For a few days during the first month of post-natal life the dancing mice which I have studied respond definitely to sounds, but neither direct nor indirect methods of testing auditory sensitiveness furnish any evidence of it in the adult.

Brightness vision is fairly acute; color vision is poorly developed. I have some evidence of the discrimination of red and blue, and of red and green, but no evidence that blue and green can be distinguished. In visual discrimination the mice apparently depend upon brightness differences.

The behavior of the dancing mouse is readily modifiable. Choice, by exclusion, of one of two objects which differ in brightness, with electrical stimulation in the case of a wrong choice, indicates that from 40 to 100 repetitions of an experience is necessary for the formation of a perfect habit. Such a modification of behavior lasts for from two to five weeks.

Modifications of behavior occur more rapidly in the male than in the female. Individual differences in plasticity and in the permanency of modification are marked.

There is little evidence of any form of imitative tendency in behavior.

5 (148)

On the motor activities of the alimentary canal after splanchnic and vagus section.

By **W. B. CANNON.**

[*From the Laboratory of Physiology in the Harvard Medical School.*]

In this investigation one series of animals was studied with only

splanchnic nerves cut, and another series with only vagus nerves cut, and a third series with an entire severance of vagi and splanchnics. The animals used were cats.

After the observations the movements of the various parts of the alimentary canal were studied by means of the shadows cast on a fluoroscope when food mixed with bismuth subnitrate had been fed and the animals exposed to the X-rays.

Movements of the esophagus. — Splanchnic section resulted in no deviation from the normal. Bilateral vagus section resulted in the well-known paralysis of the thoracic esophagus. Swallowed food accumulated in the esophagus, and, during the first few days after operation, food was frequently regurgitated. The regurgitation, however, did not persist; there was still a hindrance to an easy passage through the esophagus, but swallowed food reached the stomach. In one case, nineteen days after the second vagus nerve had been cut, a bolus of semi-fluid material was seen moving slowly and steadily along the lower esophagus into the stomach. Peristalsis alone could have done this. A distinction must be drawn between the immediate paralyzing effect on the esophagus of cutting the vagi, and the later partial or almost complete recovery of efficiency by a local mechanism in the lower esophageal wall.

Movements of the stomach. — Splanchnic section caused no alteration from the normal movements. The immediate effect of vagus section was tardiness in the starting of gastric peristalsis after food was introduced into the stomach. There was sometimes a delay of three or four hours, and the waves, when started, were extraordinarily shallow. As time elapsed these abnormalities largely disappeared; more and more the waves started early and showed their normal vigor. Again a distinction must be drawn between the first and the later effects of vagus section.

When all the extrinsic nerves were cut the gastric waves passed at the usual rhythm, but were unlike those seen when the vagi alone were cut in being, from the first, deep and powerful contractions. After death in these cases the stomach was usually found strongly contracted.

Passage of carbohydrate and protein food from the stomach. — After total suppression of impulses through the splanchnics both carbohydrate and protein foods are discharged through the pylorus

at practically the normal rate. In the absence of impulses through the vagi and in the presence of impulses through the splanchnics the discharge of both carbohydrate and protein is notably retarded. But this retardation, especially when protein is fed, is much more marked soon after the operation than it is later. Again a distinction must be drawn between the immediate depressing effect of vagus section and the later considerable recovery of normal functioning. Although the passage of both carbohydrate and protein from the stomach remains slower after vagus section, the characteristic treatment of the two food-stuffs persists — the carbohydrate passes out much more rapidly than the protein food.

When all extrinsic nerves have been cut there is, as in the cases of vagus section alone, a difference between the immediate defect and the later partial recovery of normal function. After recovery, the carbohydrate passes the pylorus at about the same rate as when vagi alone are cut, but the protein discharge is more nearly normal when all nerves are cut than when vagi alone are severed. After all splanchnic and vagus impulses are removed a characteristic difference between the outgo of carbohydrate and the outgo of protein food from the stomach is still maintained.

Passage of food through the small intestine.—After splanchnic section the rate of transit from pylorus to ileocolic sphincter, when protein was fed, was much accelerated, and after vagus section it was much slower than normal. The rate was slower also when all nerves were cut. The variation from the normal was in all cases less with carbohydrate food than with protein.

Rhythmic segmentation of the food in the small intestine was observed in every condition of nerve section.

The persistence of characteristically different rates of discharge of protein and of carbohydrate food through the pylorus, after splanchnic section, after vagus section, and after severing both sets of nerves in the same animal, definitely proves that the control of this differential discharge is local and not mediated through the central nervous system.

6 (149)

Experimental and clinical observations upon direct transfusion of blood.

By **G. W. CRILE.**

[*From the Laboratory of Surgical Physiology, Western Reserve University Medical College.*]

By means of end to end anastomosis by suture, blood was transfused in 74 dogs. Blood was transfused, retransfused and reversely transfused over a period of a month in the same dogs. There were no aglutins or hemolysins produced, no hemoglobinuria, and no nephritis. Blood was found physiologically interchangeable. Every degree of hemorrhage, even to cessation of the arterial stream was successfully treated.

In six clinical cases of hemorrhage treated by transfusion of blood the results were the same as in the laboratory. The hemorrhage factor was eliminated.

7 (150)

On the normal peristaltic movements of the ureter.

By **D. R. LUCAS** (by invitation).

[*From the Laboratory of Biological Chemistry of Columbia University, at the College of Physicians and Surgeons, and from the Rockefeller Institute for Medical Research.*]

Our present knowledge of the peristalsis of the ureter is based essentially upon the observations of Engelmann described by him about 35 years ago. He studied the peristaltic movements by simple inspection of the ureter in dogs, cats and rabbits. According to Engelmann, the contractions of the ureter in rabbits occur at intervals of 10 to 20 seconds. There were practically no other studies of the subject until a few years ago when Fagge investigated the effect of stimulation of the hypogastric nerves upon the ureter and obtained graphic records of the peristaltic movements. He makes the surprising statement that the ureter in many cases was found to be motionless or to present slight contractions or groups of contractions recurring every 30 to 60 seconds.

For the last two years I have been engaged in experimental studies of the ureter, which were carried out in the laboratory of biological chemistry at the College of Physicians and Surgeons. Some of the results of that work I had the honor to present at a meeting of this Society in April, 1905.[1] During the past summer I have studied the course of the normal peristalsis of the ureter (of the dog) at the Rockefeller Institute, under the direction of Dr. S. J. Meltzer.

The results that I wish to report here very briefly are as follows:

In dogs narcotized with morphin the peristaltic *contractions* of the middle part of the ureter occur at intervals varying between 6 and 15 seconds. The curves representiug these contractions are of variable but generally of fairly good size. The *duration* of such a contraction may vary from 5 to 15 seconds. The variations of the size and duration of these peristaltic contractions depend upon the size of the animal, the amount of secretion of urine, and many other conditions which I shall not attempt to discuss here. But for the same animal and under the same conditions the characters of the peristaltic contractions remain in general the same for nearly the entire length of the experiment, which sometimes continued about 5 or 6 hours.

These peristaltic contractions are apparently those which Engelmann and other writers had under observation. I found however, *that the renal pelvis as well as the uppermost part of the ureter exhibits peristaltic contractions of another kind;* they are small, of short duration and occur as frequently as every 2 or 3 seconds.

In some animals, in which the contractions from the middle part of the ureter presented fairly large curves, it frequently happened that these curves were superimposed by finer undulations.

From the lower end of the ureter only a few tracings were obtained. Judging from this restricted experience it would seem that in the lower end also the small and more frequent contractions predominate.

Anesthetics, *e. g.*, chloroform or ether, exercise pronounced effects upon the peristaltic movements of the ureter. The small

[1] *Proceedings of this Society*, 1904–'05, ii, p. 61.

and frequent contractions of the ureter offer a greater resistance to the effects of the anesthetic. It sometimes happened that after the administration of an anesthetic the large contractions of the middle part of the ureter disappeared while the superimposed undulations persisted. The same sometimes occurred after prolonged experimentation. The small and frequent undulations are apparently more resistant to fatigue, also, than the larger contractions.

8 (151)

Gastric peristalsis under normal and certain experimental conditions.

By JOHN AUER.

[*From the Rockefeller Institute for Medical Research.*]

The published observations upon gastric peristalsis in rabbits all seem to show that this organ, under so-called normal conditions, is practically inert. By means of the method to be described, it will be shown that the organ mentioned, under more truly normal conditions, shows active movements. The fault lay with the method; the profound inhibitory effect which opening of the peritoneal cavity exercises upon some of the abdominal viscera was not considered.

But operation is by no means necessary in order to study gastric motility in the rabbit. If a well-fed rabbit is stretched out on its back and the hair of the epigastrium clipped, any observer may see active gastric peristalsis under a closer approximation to physiological conditions than the saline bath affords. Mere inspection of the abdomen now shows that the stomach is far from inert. A short time after preparing the animal, peristaltic waves are seen coursing over the stomach from left to right, increasing in strength as the pyloric third is approached. These waves are easily registered by placing a tambour over the stomach region to be studied and connecting it with a writing tambour or manometer. The writing tambour registers not only the change in volume of the stomach part it overlies, but also the respiration of the animal; in many cases, with delicate adjustment of the writing pen, the heart beats are also marked.

That gastric peristalsis may thus be observed under almost normal conditions is not known, so far as I am aware.

Some of the results obtained by this method are as follows:

1. As a rule the stomach shows no sign of motion for a little while after the animal is stretched out.

2. After a few minutes a shallow constriction appears near the fundus and travels to the right over the stomach, becoming deeper as it progresses in that direction. The wave causes marked bulging of the pyloric third after peristalsis is well established.

3. Ether given by inhalation through the nose causes usually an immediate stoppage of gastric motion for a varying length of time. After that, peristalsis is reëstablished and continues even though the ether be pushed so that the corneal reflex becomes sluggish. Ether given through the trachea by means of a cannula has no inhibitory effect upon gastric peristalsis.

4. Curare injected intravenously does not abolish gastric peristalsis so long as artificial respiration is maintained. Stoppage of respiration causes cessation of the stomach movements. After resuming ventilation of the lungs a number of minutes elapse before gastric peristalsis again appears.

5. Section of both vagi in the neck causes stoppage of gastric peristalsis at once; tracings taken after thirty minutes, or after two, four or twenty hours show no detectable movements of the stomach.

6. The stomach of a rabbit that has fasted for twenty-four hours shows as a rule a marked diminution of the waves in strength and frequency, or none at all. Feeding reëstablishes peristaltic movements.

7. Opening the abdominal cavity causes cessation of the stomach movements for an indefinite period.

8. A moderate dose of morphin injected subcutaneously abolishes gastric motility for many minutes.

9 (152)

Reflex inhibition of the cardia in rabbits by stimulation of the central end of the vagus.

By **S. J. MELTZER** and **JOHN AUER**.

[*From the Rockefeller Institute for Medical Research.*]

At the last meeting of this Society[1] we reported that by stimulation of the central end of the vagus a tetanic contraction of the entire esophagus can be produced in dogs and cats but not in rabbits. We wish to report now that in continuation of these studies we found that *stimulation of the central end of the vagus causes a distinct inhibition of the cardia in rabbits.* The cardia of the rabbit is normally contracted in a moderate degree. Furthermore at each deglutition the peristaltic movements of the esophagus terminate in a characteristic contraction of the cardia — it sinks into the stomach. Finally after a stimulation of the peripheral end of the vagus the cardia contracts in the same characteristic way. We found that these three states of contraction can be definitely inhibited by a stimulation of the central end of the vagus. In the first place the cardia relaxes — bulges up during such stimulation. In the second place if deglutition occurs the cardia never contracts so long as the central end of the vagus is being stimulated. Finally the interruption of the stimulation of the peripheral end of the vagus does not bring on a contraction of the cardia if during this time a stimulation of the central end is going on.

10 (153)

Continuous anesthesia by subcutaneous injection of magnesium sulphate in nephrectomized animals.

By **D. R. LUCAS** and **S. J. MELTZER**.

[*From the Rockefeller Institute for Medical Research.*]

In the paper dealing with the anesthesia produced in animals by subcutaneous injection of magnesium salts Meltzer and Auer stated that animals which urinated frequently had the better chance for recovery, and that urination probably carries off some of the

[1] *Proceedings of this Society*, 1905–'06, iii, p. 74.

salt and prevents its fatal accumulation in the blood. On the basis of this assumption a series of experiments were carried out in which the anesthetic effects of subcutaneous injections of magnesium sulphate were studied in nephrectomized rabbits. The results briefly stated were as follows:

A dose of 0.8 gram of the salt per kilo of rabbit is sufficient to put the animal within a short time into deep anesthesia. This is less than half the dose that is required to anesthetize a normal rabbit. Furthermore, the nephrectomized rabbits thus anesthetized remained in a more or less comatose, paralyzed state until death, which did not occur earlier than in the control nephrectomized animal; in other words the animals remained in a state of anesthesia lasting sometimes two days and longer. Frequently the animals recovered slightly some hours after the injection, to sink soon again, however, into a deep stupor which lasted until death. The described effect was the same whether the above mentioned quantity of salt was given in one dose or was administered in fractions.

These facts demonstrate that elimination of the injected magnesium salt occurs mainly through the kidneys and that the elimination begins pretty soon after the injection. Hence when the kidneys are absent and practically no elimination takes place a smaller dose is sufficient to bring on the anesthesia, and it makes no difference whether the quantity is given at once or in small doses at varying intervals. Furthermore, the anesthesia is long lasting and continuous, as the salt cannot leave the body.

These results are especially interesting as they are in sharp contrast to the behavior of strychnin in nephrectomized animals. According to the experiments of Salant and Meltzer the toxic and the fatal doses of strychnin are the same for nephrectomized rabbits as for normal ones. Furthermore, when strychnin is given in subminimum doses nephrectomized animals can stand as much as three times the lethal dose. Finally the animal either dies from the effects of strychnin or recovers completely; a continuous long lasting convulsive state never occurs after any dose of strychnin in nephrectomized animals.

11 (154)

Remarks on and exhibition of specimens of a metastasising sarcoma of the rat.

By **SIMON FLEXNER** and **J. W. JOBLING.**

[*From the Rockefeller Institute for Medical Research.*]

The specimens which the authors exhibited consisted of a mixed cell sarcoma of the seminal vesicle of a white rat which has been transplanted successfully into a series of white rats. The original tumor, which was found in a rat dying spontaneously in the laboratory was as large as a walnut. Its surface was covered with peritoneum and its consistence was firm. Thus far it has been transplanted to full-grown and young rats both by subcutaneous and by intraperitoneal inoculation. The feature of the tumor which we wish especially to emphasize are the large and numerous metastases which have appeared in the inoculated rats. The rat exhibiting the original tumor did not show visible metastases. But in the animals which have succumbed after successful inoculation, the metastases have been numerous and of large size. They have appeared in the lungs and kidneys, and in one instance, following intraperitoneal injection, in the ribs and intercostal muscles. As the specimens show, the nodules in the lungs and kidneys may reach large dimensions, taking in a segment of the kidney or an entire lobe of the lungs. The animal in which matastases existed in the intercostal muscles showed large nodules in the lungs; in this animal a growth from the lung into the pericardium, and from the pericardium into the heart wall, took place. The secondary tumors have the same structure as the primary tumors. They are made up of spindle-shaped and polygonal cells, the latter being often of large size, with lobed or irregular nuclei. Intercellular substance is present, and it is in places fibrillated.

The epicardium in the rat in which growth occurred in the myocardium, showed invasion of the serosa by the sarcomatous cells, spreading doubtless from the nodule mentioned and causing sarcomatosis of the serous membrane. This tumor is being further transplanted and studied in its biological relationships.

12 (155)

The influence of water on gastric secretion and the chemical affinity of mucus for HCl in the stomach.

By **N. B. FOSTER** and **A. V. S. LAMBERT.**

[*From the Laboratory of Biological Chemistry of Columbia University, at the College of Physicians and Surgeons.*]

Pawlow called attention to water as a stimulant of gastric secretion but the degrees and limitations of stimulation produced by water in food Pawlow has not recorded. Using dogs with Pawlow fistulas, it was observed that with definite amounts of cracker meal as food, the amount and rate of gastric secretion depend to some extent on the amount of water given the dog with his meal, *i. e.*, when small amounts of water are given, the secretion is slow and scanty. If larger quantities of water are mixed in the food the secretion is more abundant.

The degree of acidity of gastric juice depends upon the *amount* of secretion. When this is considerable it is much more acid than when the secretion is scanty. Pawlow is of the opinion that the degree of acidity of the gastric juice is constant; this can hardly be correct, however, for the total acidity changes from hour to hour. The proportion of *free* acid depends upon the amount of mucus secreted, since mucus protein like other proteins combines with HCl. Mucus in the presence of pepsin combines with HCl to a considerable extent and undergoes digestion, with formation of proteoses.

13 (156)

The action of the electric current on toxin and antitoxin.

By **CYRUS W. FIELD** and **OSCAR TEAGUE.**

[*From the Research Laboratory of the Department of Health, of New York City.*]

In the early days of antitoxin it was thought that it might be possible to obtain antitoxin by passing an electric current through toxin. It was soon realized, however, that the fluid around the anode neutralized toxin by virtue of the acid formed about this

pole, and not because true antitoxin had been formed. It was not until 1904 that any attempt was made to determine the nature of the electric charge carried by particles of toxin or antitoxin; this research, done in Von Behring's laboratory by Romer, gave only negative results. Again in 1905, Biltz, Much, and Siebert, working in the same laboratory were unable to decide this question.

The failure of these workers was due, we believe, to the disturbing influence of the products of electrolysis. To eliminate this factor we substituted for the U-shaped tube used in the above experiments three beakers connected by agar-filled tubes, semicircular in shape and about 20 cm. long and 1 cm. in diameter. The middle beaker, into which both agar tubes dipped, contained the toxin or antitoxin to be tested; the end beakers held the platinum electrodes surrounded by distilled water, which was changed every half hour during the passage of the current. At the end of four hours, the agar was removed from the tubes, chopped into fine pieces and allowed to stand for one hour in distilled water. The agar was then removed by filtering through gauze and the toxic or antitoxic value of the fluid determined by tests on guinea pigs.

The results of our experiments were decisive. Both toxin and antitoxin particles were found to travel toward the cathode and must therefore carry positive charges. This holds true when the fluid tested is made either acid or alkaline in reaction.

Since a true chemical reaction can take place only between ions carrying charges of opposite sign, the fact that toxin and antitoxin are both electropositive would indicate that the combination of these two substances represents not a chemical union, but rather the adsorption of one colloid by another.

14 (157)

Nuclein metabolism in a dog with an Eck fistula.

By **J. E. SWEET** and **P. A. LEVENE**.

[*From the Rockefeller Institute for Medical Research.*]

A dog with an Eck fistula was maintained in nitrogenous equilibrium on a diet consisting of cracker meal, plasmon and lard, and the following chemical observations were made:

1. The output of uric acid was compared with that of a normal dog. An increase in the output was noted.

2. The influence of nuclein, nucleic acid and of adenin on the uric acid elimination was studied. It was observed that all these substances caused an increase in the uric acid elimination.

3. The fate of thymin ingested with the food was investigated. The greater part of the ingested thymin was recovered from the urine.

4. An attempt was made to find thymin in the urine of the same dog after feeding on nuclein and on nucleic acid. The endeavor was not successful.

5. The influence of a diet containing a small proportion of protein but abundant in calories was studied. It was noticed that this diet occasioned an increase in the uric acid output.

6. The influence of fasting on the uric acid output was observed. It was noted in the course of the fast that the uric acid elimination was above the normal.

15 (158)

On the fractionation of agglutinins and antitoxin.

By **R. B. GIBSON** and **K. R. COLLINS.**

[*From the Research Laboratory of the Department of Health, of New York City.*]

E. P. Pick in 1901 associated a number of anti-substances individually with the one or the other of the two serum globulin fractions of the Hofmeister classification. In the pseudoglobulin [3.4 to 4.6 sat. $(NH_4)_2SO_4$ solution[1]] group of antibodies he placed the diphtheria and tetanus antitoxins and the typhoid agglutinin of horse serum; the lower or euglobulin fraction (2.9 to 3.4 sat.) comprises diphtheria and tetanus antitoxin and cholera lysin in the goat, typhoid agglutinin in the goat, rabbit and guinea pig, and finally cholera agglutinin in the horse and goat. It becomes possible, according to Pick, to separate the individual specifically reacting anti-substances by fractioning appropriate mixtures of sera. Such a possibility suggested the application of this method to the further study of certain anti-bodies, especially of the relation of specific and group agglutinins developed by immunization against a single strain of organism. Preliminary experiments in the course of our inves-

[1] The degrees of saturation, as here expressed, indicate a concentration equivalent to a content in 10 c.c. of solution of 3.4 c.c. and 4.6 c.c. of saturated ammonium sulphate solution respectively.

tigation indicated the unreliability of Pick's differentiation, and attention was accordingly directed to the actual possibility and practicability of distinguishing between anti-bodies by fractionation of the globulin. The availability of poly-agglutinative sera for the work gave a chance for making numerous and extended observations of the distribution of these anti-bodies in the fractions.

It was found repeatedly in experiments with rabbit and goat sera that the agglutinins for the dysentery group of organisms (Flexner Manila and Shiga), typhoid, coli and cholera, were not confined to either the pseudoglobulin or the washed [with 3.4 sat. $(NH_4)_2SO_4$ solution] euglobulin fractions; they were either split by the fractioning, the major portion occurring in the pseudoglobulin, or almost the entire amount of the agglutinating substances recovered were in this higher fraction in the original quantitative proportion to one another. With anti-dysentery horse serum, the dysentery (Shiga and Flexner) and coli agglutinins were fairly quantitatively though not qualitatively split between the pseudo- and euglobulin fractions, the latter containing the lesser amount. With an anti-cholera and anti-typhoid horse serum, the pseudoglobulin (two experiments) and also the filtrates from two additional 3.6 and 3.8 saturation precipitations contained the bulk of the agglutinins. In subsequent experiments with sera from other bleedings as well as with the sera used above, the typhoid agglutinin was divided between the two fractions with a somewhat larger proportion occurring in the pseudoglobulin.

It is apparently difficult to control all the conditions under which experiments of this type are made; absolutely constant results at times cannot be obtained on successive repetition of the work.

The results of exhaustion experiments on the two globulin fractions were the same as those that would be obtained in the use of the native serum, and failed to give any reason for believing that we were dealing with a separation of group and specific agglutinins through fractioning.

Precipitation of anti-diphtheria goat serum showed that about half the antitoxin remained in the pseudoglobulin; practically none was found in the euglobulin while the 3.4 saturated $(NH_4)_2SO_4$ solution washings contained the balance.

The results of the work thus far accomplished have demon-

strated the untrustworthiness of any such differentiation of the anti-bodies as those contained in the euglobulin and those of the pseudoglobulin. No evidence has been adduced from our experiments to show that the agglutinins developed in the rabbit, goat and horse can be classed as belonging to either globulin, or that these anti-bodies can be separated from one another by ammonium sulphate fractioning of polyagglutinative sera.

16 (159)

Further observations of the effects of ions on the activity of enzymes.

By **WILLIAM N. BERG** and **WILLIAM J. GIES.**

[*From the Laboratory of Biological Chemistry of Columbia University, at the College of Physicians and Surgeons.*]

Previous communications from this laboratory[1] have made it evident that peptolysis of *fibrin* is unequal in rate and extent in acid solutions of equipercentage, equinormal (isohydric), equimolecular, or equidissociated (isohydrionic) concentration. The same may be said of tryptolysis of the same protein in a series of bases of analogous concentrations.

We have found that the sequence of zymolysis, both in rate and extent in a given group of acid or basic solutions, varies considerably with the nature of the protein. This fact makes it impossible accurately to formulate statements regarding various phases of peptolysis or tryptolysis without specifying the particular protein involved in the process; it also renders doubtful various general conclusions of common acceptance pertaining to digestion that have been derived, in one research or another, from the use of a single protein. A study of the peptolysis of *many proteins*

[1] Gies: *American Journal of Physiology*, 1903, viii (Proceedings of the American Physiological Society, 1902, p. xxxiv); *the same journal*, 1903, ix (Proceedings of the same Society, 1903, p. xvii); Gies and collaborators: *Biochemical Researches*, 1903, i, pp. 61–63. Also Berg (communicated by Gies): *Science*, 1906, xxiii, p. 335 (Proceedings of the Section of Biological Chemistry of the American Chemical Society in affiliation with Section C (Chemistry) of the American Association for the Advancement of Science, 1905); *Proceedings* of the American Association for the Advancement of Science, 1906, p. 331.

in a given series of acid solutions has therefore been undertaken, and an effort will be made to extend the observations to the tryptolysis of the same proteins in a given series of basic solutions.

The speed and extent of both peptolysis and tryptolysis are resultants of conflicting influences. In the case of peptolysis, for example, the hydrogen ions in a given acid solution are always essential and positive factors, whereas the accompanying anions or molecules or both appear to be, *as a rule*, non-essential and inhibitory factors. This conclusion is warranted by such results as the following, taken from our records of an experiment in which 1 gram quantities of fibrin were used in 100 c.c. portions of solution at 40° C.:

	A. Control solutions (without pepsin).		B. Digestive mixtures, containing equal amounts of pepsin and HCl(*m*/20), with different proportions of H_2SO_4.						
Acid solutions:	*a*	*b*	1	2	3	4	5	6	7
m/10HCl (c.c.)	100	——	50	50	50	50	50	50	——
m/10H_2SO_4 (c.c.)	——	100	——	10	20	30	40	50	50
Water (c.c.)	——	——	50	40	30	20	10	——	50
Total volume (c.c.)	100	100	100	100	100	100	100	100	100
Weight of residue (mgs.)[1]	960	994	162	439	430	500	553	582	695
Gram-atoms of H•, per 1,000 liters.	94	116	48	62	73	85	96	107	61
Concentration of H_2SO_4	——	*m*/10	——	*m*/100	*m*/50	*m*/33	*m*/25	*m*/20	*m*/20

That acid molecules are not necessarily inhibitory in peptolysis is shown clearly by the appended results of an experiment similar to the one just referred to, but in which *acetic acid* was used instead of sulfuric acid. In the mixtures referred to below the dissociation of the acetic acid was slight and negligible:

	A. Control solutions (without pepsin).		B. Digestive mixtures, containing equal amounts of pepsin and HCl (*m*/20) with different proportions of CH_3COOH.						
Acid solutions:	*a*	*b*	1	2	3	4	5	6	7
m/10 HCl (c.c.)	100	——	50	50	50	50	50	50	——
m/10 CH_3COOH (c.c.)	——	100	——	10	20	30	40	50	50
Water (c.c)	——	——	50	40	30	20	10	——	50
Total volume (c.c.)	100	100	100	100	100	100	100	100	100
Weight of residue (mgs.)[2]	961	961	198	194	196	193	187	191	945
Gram-atoms of H•, per 1,000 liters.	94	1.3	48	48	48	48	48	48[3]	0.9
Concentration of CH_3COOH	——	*m*/10	——	*m*/100	*m*/50	*m*/33	*m*/25	*m*/20	*m*/20

[1] Our data for neutralization precipitates (acidalbumin) and proteoses and peptones are omitted for brevity's sake. They accord with the data for undigested residues.

[2] Our data for neutralization precipitates (acidalbumin) and proteoses and peptones are omitted for brevity's sake here also. They are in accord with the data for undigested residues.

[3] Although the H• concentration of an *m*/20 acetic acid solution is approximately

The results of this and similar experiments with acetic acid throw new light on the well known fact that peptolysis is almost negative in solutions of acetic acid alone. This lack of peptolytic efficiency on the part of acetic acid is apparently due to the low hydrion concentration of acetic acid solutions. The acetic acid molecules and anions, in the proportions above indicated, seem to be practically inert. It is obvious that peptolysis is neither favored nor interfered with materially by moderate amounts of acetic acid, a fact which suggests that the purely *chemical* phases of the normal gastric digestive process are practically unaffected by vinegar. *Secretory* conditions, however, are no doubt modified.

Experiments in this and other connections will shortly be completed before the detailed publication of our results.

0.9 gram-atom per 1,000 liters, the dissociation of the same proportion of acetic acid in an *m*/20 hydrochloric acid solution is reduced to 0.018 gram-atom per 1,000 liters. For this reason the $H^{\bullet}$ concentration of the mixed acids is practically that of the hydrochloric acid (*m*/20) in each case. The dissociation of the hydrochloric acid was not materially affected by the acetic acid in the mixtures used.

Nineteenth Meeting.

Schermerhorn Hall, Columbia University. December 19, 1906. President Flexner in the Chair.

17 (160)

An experiment on the localization problem in the egg of Cerebratulus.

By **NAOHIDÉ YATSU.**

[*From the Zoological Laboratory of Columbia University.*]

In the egg of *Cerebratulus marginatus* Zeleny found, in separating at the 8-cell stage the upper animal blastomeres from the lower vegetative ones, that the third cleavage plane cuts off the basis of entoderm from that of ectoderm. I repeated the same experiment on the egg of *Cerebratulus lacteus* and found that the condition is somewhat different. In this form the third cleavage does not always separate the entodermic stuff from the ectodermic, so that the embryo from the animal-half sometimes invaginates and sometimes does not. But in shifting the third cleavage plane to the equator by compressing the egg immediately after the first division (in doing this, the second cleavage is suppressed until pressure is relieved, the third cleavage of the normal egg appearing next to the first) and in separating the animal-half from the vegetative, the former always gave rise to the embryos without gut, anenterons. From this it may be concluded that in the egg of *Cerebratulus lacteus*, a little before or at the time of the third cleavage, the entodermic basis extends farther above than that of *Cerebratulus marginatus.*

18 (161)

Experiments upon the total metabolism of iron and calcium in man.

By **H. C. SHERMAN.**

[*From the Havemeyer Laboratory, Columbia University.*]

Each of the experiments was of three days duration and the same healthy man served as subject throughout. On a diet of

crackers and milk, which furnished 0.0057 gram iron and 2.65 grams calcium oxide (Exp. I), there was equilibrium with respect to iron, and a storage of calcium. When the diet consisted of crackers and egg-white with 0.0065 gram iron and 0.14 gram lime (Exp. II), or of crackers alone with 0.0071 gram iron and 0.13 gram lime (Exp. III), there were losses of both iron and calcium. These losses occurred through the intestine, but were evidently not due to intestinal putrefaction, since the ratio of sulphur in ethereal to that in simple sulphates in the urine was determined in Exp. III and found to be as 1 : 25. The results appear to confirm the suggestion of Von Wendt that a deficiency of calcium in the diet may lead to a loss of iron as well as of calcium from the body. There was a slight tendency toward diarrhea in each of the periods in which loss of iron and calcium occurred. The iron requirement evidently varied greatly, the average daily output for three experiments being 5.5, 8.7 and 12.6 milligrams respectively.

The lime requirement was found by further experiments (IV and V) to be about 0.75 gram of calcium oxide per day.

The experiments were conducted at Columbia University in coöperation with the U. S. Department of Agriculture and will be described in detail in a bulletin of the Office of Experiment Stations of that department.

19 (162)

The cause of the treppe.

By **FREDERIC S. LEE.**

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

The treppe is usually ascribed to increased irritability caused by activity. The cause of the increased irritability has remained obscure. In studying the depressing action on muscle of its fatigue substances the author often observed augmentation of activity instead of depression. A more careful investigation of this phenomenon shows that it may be produced by all of the three recognized fatigue substances — namely, carbon dioxide, monopotassium phosphate, and paralactic acid. When a muscle is irrigated with an indifferent fluid containing one of these substances in

small quantity, and compared with its mate irrigated only by the indifferent fluid, a fatigue record being made from both, more intense contractions frequently occur in the poisoned muscle at the beginning of the experiment, and may last until exhaustion sets in. When a fatigue record is being made from a muscle with the circulation intact, intravenous injection of a fatigue substance causes augmentation of contraction. The author concludes that the treppe is due to the augmenting action of fatigue substances in small quantities — the same substances which in larger quantities cause depression or fatigue.

An excellent mode of demonstrating the augmenting action of CO_2 in the cat is to record the contractions of the tibialis anticus in the living animal, and while the record is being made, to clamp the trachea. A marked treppe follows.

If two corresponding muscles be compared, one with the circulation intact, and the other with its arteries ligated, the latter muscle performs more intense contractions and exhibits a more rapidly developing treppe, owing to the accumulation of fatigue substances.

The chemical theory of the treppe is able to explain several other known phenomena. The author has experimented on both frogs and cats. The augmenting action of the fatigue substances seems to be observed even when curare is employed.

20 (163)

The influence of the red corpuscles upon the viscosity of the blood.

By **RUSSELL BURTON-OPITZ.**

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

The method by means of which the following determinations of the viscosity were made has been described in Pflüger's Archiv, Vol. 82, p. 464.

Having determined the coefficient for fresh ox serum at 37° C. the serum was gradually concentrated by the addition of definite quantities of red blood corpuscles (washed). The viscosity of the "blood" was tested after each addition of corpuscles.

The following data may serve as examples:

	Spec. Grav.	No. of Red Corpuscles.	Viscosity Coefficient.
Serum.....	1.0248	——	2397.7
S + 30 c.c. corp	1.0382	4,000,000	1442.9
S + 30 c.c. corp.....	1.0467	4,700,000	1009.3
S + 30 c.c. corp.....	1.0524	5,700,000	851.6

Thus, the increase in the number of red corpuscles caused a corresponding increase in the viscosity. It is also obvious that the red corpuscles constitute the principal factor in determining the viscosity of the blood.

21 (164)

A new recording stromuhr, with demonstration.

By **RUSSELL BURTON-OPITZ.**

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

The cylinder of this stromuhr is placed horizontally and carries below its floor a valve, by means of which the inflowing blood can be diverted alternately into the right and left half of the instrument. The piston within the cylinder moves back and forth, therefore, in a horizontal direction and records its movements by means of a pulley arrangement and a writing lever upon the smoked paper of a kymograph.

On account of its great sensitiveness, and the possibility of low adjustment, this stromuhr is especially fitted for measuring the blood flow in the veins.

The instrument has been used by the author in testing possible vaso-motor reactions in the pulmonary circuit. It was connected with the vein draining the middle lobe of the left lung. The nerves in the vicinity of the ganglion stellatum were stimulated. So far the experiments have given negative results.

22 (165)

The influence of gelatin upon the viscosity of the blood.

By **RUSSELL BURTON-OPITZ.**

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

Solutions of gelatin (1000 : 50) were introduced intravenously after the normal viscosity of the blood had been determined. It was found that the injections resulted in a very prompt increase in the viscosity. The following data may serve as examples :

Specific Gravity.		Viscosity.	
Before Inj.	After Inj.	Before Inj.	After Inj.
1.0565	1.0543	836	772

23 (166)

The hemolytic effects of organ and tumor extracts.

By **RICHARD WEIL** (by invitation).

[*From the Huntington Fund for Cancer Research of the General Memorial Hospital, Loomis Laboratory, Cornell University Medical College, New York City.*]

The object of the present investigation was to determine the causes of, or factors contributing to, the secondary anemias of malignant tumors. The material made use of was supplied by Dr. Beebe, and consisted of sarcomata artificially implanted in dogs. The method was to crush these tumors in a mortar, mix them with ten times their weight of salt solution, and then stir mechanically for several hours. The hemolytic effect of this extract was tested on a 1 per cent. emulsion of the red cells of dogs. Preliminary experiments were made with extracts of kidneys of dogs prepared in the same fashion. It was found that the cause of the variability in the hemolytic effect of organ extracts, which has been noted by previous observers, is the varying admixture of blood. Kidneys prepared bloodlessly, by perfusion with salt solution, are hemolytic only in very low dilution, and after a long latent interval. Kidneys suffused with blood are as a rule very much more active ; occasionally less so. The effects of blood have been analyzed by the separate addition of serum, emulsions of white cells (from artificial abscesses), and of red cells after washing, to the bloodless

kidney extract. In each case it was found that hemolysis was inhibited. The question therefore arises, why are kidneys suffused with blood as a rule more actively hemolytic than the bloodless organs? If their extracts are centrifuged, and all the solid particles, including the red cells, removed, it is found that the extracts are still deeply stained by hemoglobin. This is due to the destruction and solution of red cells, which is inseparable from the process of preparing the extract. The next step, therefore, was to determine the effect of adding red cell constituents to the bloodless organ extracts. This was accomplished by adding red cells to distilled water, and then bringing the solution to the strength of normal salt solution. Such a solution adds very markedly to the hemolytic power of the organ extract. Its manner of action seems to resemble that of complement, inasmuch as it is capable of breaking up the red cells only after a preliminary treatment with the organ extract.

Tumors were investigated in the same manner as the kidneys. It was found that the non-necrotic tumors are somewhat more hemolytic than are the kidneys, owing possibly to their blood content. They act, however, in other ways precisely like the latter, their action being diminished by the addition of serum and of white cells, and of being increased by the red cell extract.

Necrotic areas of tumors are extremely hemolytic, even up to dilutions of two to four hundred. This hemolytic activity is not affected by the addition of the blood components.

An experimental study was made of the action of a necrotic organ, by ligating the vessels and removing the organ after several days. The extract was hemolytic in a dilution of one in 6,000. It acted in other respects like the extract of necrotic tumors.

24 (167)

The enzymotic properties of diplococcus intracellularis.

By **SIMON FLEXNER.**

[*From the Rockefeller Institute for Medical Research.*]

The brief vitality of many of the cultures of diplococcus intracellularis is a point of differential importance. Many strains, grown on a favorable medium, unless transplanted to a fresh

medium, do not survive beyond two or three days. Cultures three days old show marked degenerations, and the latter increase rapidly with age until, at the end of five or six days, or even earlier, no normal cocci persist. As degeneration progresses, loss of staining power and disintegration ensue, until finally, staining capacity is lost and a formless detritus remains.

The changes in the diplococcus are associated with the action of an enzyme which brings about the disintegration. This enzyme does not exhibit the usual properties of a proteolytic ferment: it does not liquify gelatin or coagulated serum. The degree and rapidity of its action varies with its concentration; at least a heavy suspension of the cocci in salt solution, kept at 37° C., undergoes dissolution more rapidly and completely than a weaker suspension. The vitality of the cultures is associated with the degree of autolytic alterations in the suspensions: cocci in the weak suspensions survive longer than in the stronger ones. At lower temperatures — 2°C. — disintegration of the cocci either does not take place at all or progresses much more slowly. Under the latter conditions more cocci survive in the strong than in the weak concentrations, although even here the vitality is a brief one.

Potassium cyanide restrains the action of the ferment which tends to disintegrate the diplococci; after removal of the cyanide, dissolution sets in. Heating the diplococci to 65° C. prevents or reduces the dissolving power of the intracellular enzyme.

The brief vitality which the diplococcus exhibits, as grown upon the usual media, and in salt suspensions, is associated with a deficiency of calcium in the media. If the diplococcus is suspended in Ringer's solution it survives, in concentrated suspensions, for 15 days at least, and if it is grown upon serum-glucose-agar to which calcium carbonate has been added, the period of viability is considerably greater than this. The diplococcus suspended in Ringer's fluid and killed by heat (60° C.) or toluol, undergoes autolysis.

The enzyme acts upon the dead cocci — probably not upon the living germs. Diplococci killed by heat (50° to 55° C.) undergo autolysis; but when the cocci are killed by the addition of toluol autolysis is accelerated. A heavy suspension of the diplococci in salt solution, under toluol and kept at 37° C., may be disintegrated in four hours.

The enzyme of the diplococcus acts energetically upon other bacteria, bringing about their dissolution. It acts upon *B. typhosus*, *B. coli communis*, *B. pyocyaneus*, *B. anthracis*, *M. catarrhalis*, and to a less degree and more slowly upon *Staphylococcus aureus*.

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On the supposed existence of efferent fibers from the diabetic center to the liver.

By **J. J. R. MACLEOD** and **C. E. BRIGGS**.

[*From the Physiological Laboratory, Western Reserve University.*]

To explain the causation of those forms of glycosuria which follow stimulation of the central end of sensory nerves and *piqûre* of the medulla, it is commonly believed that there is a diabetic center in the medulla from which efferent impulses are transmitted to the liver causing the glycogen in this organ to become so rapidly converted into dextrose that hyperglycemia and glycosuria follow. Since section of the vagi does not prevent these forms of glycosuria, it is thought that the efferent impulses travel by the upper portion of the spinal cord and the greater splanchnic nerves.

That increased production of dextrose by the liver is the immediate cause of the glycosuria, there is no doubt, but the evidence that it is by nervous impulses transmitted from the medulla to the liver along the above path that this hyperglycogenesis occurs is very meager.

The evidence *in favor* of such a view is as follows:

1. Puncture of the floor of the fourth ventricle does not cause glycosuria if the splanchnic (greater) nerves, or the upper thoracic spinal nerves, or the spinal cord above the first thoracic nerves be cut (Eckhard, Marc Laffont, etc.).

2. Irritation of the cervical spinal cord, or of the upper thoracic sympathetic ganglia causes glycosuria (Pavy, Schiff).

Against such a view stands the fact that stimulation of the splanchnic nerves does not cause glycosuria (Cf. Pflüger).

As has been shown by us, and by other workers, the reducing power of the urine of dogs is, within certain limits, no index of the amount of sugar in the blood. Now, very little of the above

evidence is based on observations of the amount of sugar in the blood, this being assumed to be increased whenever the urine strongly reduces. We have accordingly undertaken a reinvestigation of the foregoing evidence but have examined the reducing power of the blood instead of that of the urine.

Of certain of our results, viz., those relating to the influence of nicotin and of lowered blood pressure on the blood sugar, we have already made preliminary communication.[1, 2]

In the present communication are reported the results which we have so far obtained on the changes in the amount of sugar (reducing substance) of the blood resulting from stimulation of the spinal cord at various levels, and from stimulation of the splanchnic nerves. The sugar analyses were performed by the method of Waymouth Reid.[3]

The following table gives the averages of the results so far obtained:

Nature of Experiment.	No. of Exps.	Blood Sugar in gm. Per cent. Before Stimulating. No. of Analyses Included in Averages.	Blood Sugar in gm. Per cent. After Stimulating. No. of Analyses Included in Averages.
Stimulation of peripheral end of one splanchnic nerve, the opposite splanchnic and the vagi being cut	6	0.133 (9)	0.145 (9)
Stimulation of cut spinal cord below the cervical region	7	0.163 (8)	0.160 (12)
Stimulation of lower cervical region of spinal cord.			
A. With cord cut	1	0.140 (2)	0.236 (2)
B. With cord uncut	2	0.189 (3)	0.276 (4)
C. With oxygen freely administered by Hirch's method[4]	2	0.140 (2)	0.157 (6)

It will be seen that no hyperglycemia is produced by stimulation of the splanchnic nerves, or of the spinal cord below the cervical region. In the cervical region, on the other hand, stimulation produces hyperglycemia except when oxygen is very freely

[1] Macleod and Dolley: Proceedings of the Physiological Society, *Journal of Physiology*, 1905, xxxii, p. lxiii.

[2] Macleod and Briggs: Proceedings of the Toronto meeting of the British Medical Association, *British Medical Journal*, Dec. 22, 1906.

[3] Reid: *Journal of Physiology*, 1896, xx, p. 316.

[4] Hirsch: Ueber Künstliche Atmung durch Ventilation der Trachea. Dissertation, Giessen (1905); ref., *Biophysikalisches Centralblatt*, 1905.

delivered into the trachea. By such administration it has been shown by Hirsch that the blood remains arterial even after the respiratory movements have been inhibited by curare. When the cervical spinal cord is stimulated, and especially when it is cut, the respiratory movements are very considerably interfered with so that a partial asphyxia is produced which may be the cause of the hyperglycemia.

The fact that stimulation of the cervical cord causes glycosuria cannot therefore be taken as a proof of the existence of efferent fibers which control the glycogenic function of the liver. Dyspnea may be the cause of the hyperglycemia in these cases.[1]

Regarding the other evidence, which is supposed to point to the existence of such fibers, we would point out that in all the experiments on which it is based (viz., cutting the splanchnics, or sympathetic chain, or certain nerve roots, or the spinal cord, there must have been induced by the operation, a great fall of blood pressure which, in the cases of dogs with vagal glycosuria, Dolley and the writer have shown usually to cause a marked depression in the reducing power of the urine (*loc. cit.*).

Conclusion. — When every precaution is taken to prevent asphyxia we have been unable, so far, to demonstrate the existence of any efferent fibers whose stimulation causes hyperglycemia.

[1] Underhill (*The Journ. of Biol. Chem.*, 1905, i, p. 113), explains the hyperglycemia produced by the administration of certain drugs on the same basis, viz., that they produce dyspnea by an action on the respiratory center.

Twentieth meeting.

Rockefeller Institute for Medical Research. February 20, 1907. President Flexner in the chair.

26 (169)

Experimental studies on nuclear and cell division.

By **EDWIN G. CONKLIN.**

[*From the Zoological Laboratory, University of Pennsylvania.*]

During several seasons extensive experiments were made on the segmenting eggs of *Crepidula plana*. These experiments included a study of the influence on nuclear and cell division of hypertonic and hypotonic sea water, of ether, alcohol, etc., of the lack of oxygen, of the electric current, and of pressure and shaking. The following general conclusions may be drawn from this work:

1. Under the same treatment the effects may be extremely varied, owing, probably, to the different stages of cell division acted upon.

2. A dividing cell is much more easily disturbed or rendered abnormal than is a resting one; the mitotic figure in particular is very easily altered and most of the abnormalities observed arise from this source.

3. The earlier stages of cleavage are much more easily altered than are the later ones.

4. Certain general abnormalities occur after the most varied treatment, *e. g.*, the general results both of concentration and of dilution of sea water are to produce polyasters and to prevent the cleavage of the yolk.

5. On the whole the results of the hypertonic solutions are the same whether they are produced by evaporation of the sea water or by the addition of NaCl, $MgCl_2$, or KCl to sea water; in short, these salts exert no specific action on cell division.

6. The most general modification of the mitotic figure is the production of polyasters, multipolar spindles, and as a consequence, multiple nuclei. In many cases the cells are filled with asters and irregular mitotic figures, during division, while in the resting stage they are filled with equally numerous resting centrosomes and nuclei.

7. The movements of the chromosomes are in many cases interrupted, so that they remain scattered along the spindle, while the cytoplasmic movements are frequently stopped or altered.

8. In some cases the achromatic portion of the nucleus is separated from the chromatic part, and the two may persist side by side during the resting stage of the cell; in the division stages the achromatic nuclei give rise to asters, the chromatic to chromosomes and both may divide indefinitely, giving rise to large numbers of chromatic and achromatic nuclei.

9. The most general modification of the division of the cell-body is the suppression of the cleavage of the yolk; this occurs in practically all the experiments; at the same time the cleavage may proceed more or less regularly in the protoplasmic portion of the egg. In normal eggs the first and second cleavages divide the yolk into four equal cells (the macromeres) and, from each of these, three small cells (the micromeres) are budded off.

10. If the yolk remains undivided it gives rise in certain cases to three micromeres, which have the characteristics of those formed from each of the four macromeres of the normal egg. If the yolk has divided once so as to form two macromeres, each of these may give rise to three micromeres, having the characteristics of the three quartet cells of the normal egg. In short, the number of micromeres depends upon the number of macromeres. When there are four of these as in normal eggs, the micromeres are formed in three quartets; when there are two, they are formed in three pairs; when there is but one macromere, *i. e.*, when the yolk remains undivided, the micromeres are formed singly.

11. When eggs are subjected to pressure the third cleavage which normally gives rise to the first group of micromeres, may divide one or more of the macromeres equally, thus giving rise to five, six, seven or eight macromeres. If the pressure is removed from such eggs each macromere gives rise to three micromeres in

a manner approximately normal ; again showing that the number of micromeres which may come from a macromere is constant, whatever the number of macromeres may be.

12. The results stated in the two preceding paragraphs show that the omission or the addition of cleavages does not alter the character or localization of the egg substances and that this localization, when unimpeded, determines the character of the cell division.

13. Isolated blastomeres undergo partial development, each giving rise only to the cells which it would form if still a part of the entire egg, but the general form of the cleavage mass is entire, *i. e.*, there is no open side.

14. A weak electric current destroys spindle fibers and astral rays, or prevents their formation and thus stops mitosis. It also destroys the polarity of the cell, prevents the separation of protoplasm and yolk, and may cause nuclei to migrate through the cell from one pole to another.

15. Abnormalities of mitosis may perpetuate themselves in subsequent divisions, even when the cause which first induced them is removed.

27 (170)

Heterotransplantation of blood vessels.

By **ALEXIS CARREL.**

[*From the Rockefeller Institute for Medical Research.*]

It is well known that the tissues of an animal do not grow or grow hardly at all in an animal of another species. Nevertheless, I attempted to transplant to cats, blood vessels resected from dogs, with the aim of ascertaining whether the vessels in spite of the toxic action of the cat's blood on the dog's tissue, could take over the functions of the vessels removed.

The method consisted of removing a segment of the abdominal aorta of a cat, and of reestablishing the circulation in the lower part of the aorta by interposing a segment of the jugular or carotid of a dog and suturing it to the cut ends of the aorta.

Five similar experiments were performed. In three cases, lesions of one or two anastomoses, and thrombosis of the vessel, occurred two days, ten days and thirty-five days after the operation. However, the wall of the transplanted segment remained apparently normal. In the fourth case, the transplanted segment, extirpated and examined six days after the operation, appeared to be normal and perfectly united to the ends of the aorta. On the fifth animal, a laparotomy was performed forty-eight days after the transplantation. It was found that the pulsations were normal in the abdominal aorta and the segment of carotid. The location of the anastomoses was marked by a slight hardening of the arterial wall. No dilatation of the transplanted segment was observed. The animal was kept alive and is now, seventy-eight days after the operation, in excellent condition. The pulsations of the femoral arteries remained normal.

The experiments show merely that a segment of a dog carotid which had been transplanted in a cat could act as artery for seventy-eight days at least.

28 (171)

Transplantation of the kidney with implantation of the renal vessels in the aorta and vena cava.

By **ALEXIS CARREL.**

[*From the Rockefeller Institute for Medical Research.*]

The transplantation of the kidney with implantation of the renal vessels in the aorta and vena cava consists of extirpating from an animal a kidney with its vessels, together with a patch of the aorta and vena cava; also of transplanting the kidney into the abdomen of another animal and suturing the edges of the patches to the edges of suitable openings made in the walls of the aorta and vena cava. By this patching method, the anastomoses are more safely performed than by the other methods of anastomosis. If the patch be large enough, occurrence of gangrene in the transplanted organ is practically impossible. With Guthrie, I used this method mainly on cats and obtained excellent results from the standpoint of restoration of the circulation. In dogs, on account

of the shape of the abdomen, it is difficult to prevent the occurrence of congestion of the kidney. This occurs because of compression of the renal vein between the aorta and the kidney. It could be prevented by putting the new kidney exactly at the place of the extirpated one.

This operation is not dangerous. Of seven animals operated on, six remained in good health. The seventh died of intestinal intussusception four days after the operation.

29 (172)

Secondary peristalsis of the esophagus — a demonstration on a dog with a permanent esophageal fistula.

By **S. J. MELTZER.**

[*From the Rockefeller Institute for Medical Research.*]

The peristalsis of the esophagus with which every one is familiar is that which follows an act of deglutition. About a year ago I reported to this society that experiments which I had made on rabbits demonstrated that the esophagus is capable of peristaltic movements not initiated by deglutitions. Injections of indifferent solutions or of air directly into the esophagus cause there a regular peristaltic movement. This latter form of peristaltic movement, which for the sake of brevity I shall henceforth term *secondary peristalsis*, differs from the *primary peristalsis*, the one which follows deglutition, essentially through the nervous mechanism by which it is controlled. All the movements of the complicated act of deglutition are managed by a reflex mechanism, with only one sensory stimulus for its initiation and a series of consecutive motor impulses going to every part of the long path of deglutition; it is practically a single reflex. The reflex mechanism of the secondary peristalsis, on the other hand, consists of a chain of reflexes; each part of the esophagus sends up to the center a sensory impulse started by the presence of the bolus in that part and receives in turn a motor impulse. The secondary peristalsis therefore requires the presence of some sort of a bolus within the esophagus and presupposes the integrity of the latter; whereas the primary peristalsis requires neither a bolus nor the integrity of the esophagus;

even if a large section of the latter is removed, the peristalsis appears in the lower segment in due time after each deglutition as long as the vagus nerves remain intact.

Recently secondary peristalsis was studied in the esophagus of dogs, in which animals it appeared promptly and was easily demonstrable. The bolus consisted mostly of a piece of absorbent cotton attached to the middle of a long thread, one end of which ran through an opening in the floor of the mouth and the other through an opening in the stomach. The animal was of course narcotized but anesthesia interferes greatly with both forms of peristalsis. The observations however were made when the animal recovered from the anesthesia. It was found that the bolus went down to the stomach from any part of the esophagus without being started by a preceding deglutition. The bolus had to be of a certain size; if too small it was either without effect or the effect set in late and the movement was slow and irregular. When the bolus was kept by force in one place for a long time that place lost the promptness of its irritability. It recovered this again, however, a few minutes after the removal of the bolus. I shall not enter upon further particulars except to mention the observation made by Dr. Auer and myself that section of one vagus will remove the secondary peristalsis, while the primary peristalsis is but very little affected.

The chief object of the present communication was a demonstration of both forms of peristalsis in a dog with a permanent fistula in the upper half of the cervical esophagus. I introduced into the fistula an olive-shaped body of hard rubber to which a long thread was attached. The thread ran over a rod and had a paper fan at the opposite end. When the olive-shaped body traveled down into the stomach the fan was observed to move upwards. When the olive-shaped body was placed into the lower half of the cervical esophagus it remained in that place without moving downwards. A deglutition, on the other hand, carried it down into the stomach. But when the olive-shaped body was placed into any part of the thoracic esophagus it was promptly carried down into the stomach without the aid of a preceding deglutition. When the olive-shaped body was held back by force for some time, it was not carried down spontaneously — a deglutition, how-

ever, carried it down promptly. These facts mean that the thoracic esophagus, which remained normally innervated, manifested secondary and primary peristalsis. Retention of the olive-shaped body in one place for some time fatigued the sensory nerve fibers and thus impaired the mechanism of the secondary peristalsis, but the primary peristalsis which required only intact motor nerves remained unaffected. In the cervical part, however, the innervation of the left side of the esophagus was greatly impaired or perhaps even abolished by the operation and the abnormal adhesions.

We see from the last mentioned results, therefore, that the secondary peristalsis is completely abolished, while the primary peristalsis is practically intact, which is in harmony with the above mentioned observations of Dr. Auer and myself of the effect of section of one vagus upon the secondary peristalsis of the esophagus.

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Peristaltic movements of the rabbit's cecum and their inhibition, with demonstration.

By **S. J. MELTZER** and **JOHN AUER.**

[*From the Rockefeller Institute for Medical Research.*]

The rabbit's cecum fills nearly one half of the abdominal cavity and is full of food, which has to get into it and leave it again by some moving force. Nevertheless we find in the literature practically no statement on the movements of that organ. There is good reason for it. When the abdominal cavity of a rabbit is opened the cecum as a rule shows no motion. We wish to report that according to our observations, that organ exhibits well marked and quite regular peristaltic movements; but these can be seen only in the normal animal. When a well fed rabbit is fastened on its back on a holder and the hair of the abdomen is removed, as a rule movements of the cecum can be seen sooner or later. The movements are well marked and characteristic in their appearance, and leave no doubt as to the organ in which they take place. We shall mention only a few details in this communication. As a rule, especially in well fed rabbits, the movements begin in the colon and travel towards the small gut, that is, they are antiperistaltic in

character. But frequently at the end of an antiperistalsis, after only a short interval, the wave returns and runs from the small gut towards the colon; in other words, the antiperistalsis is often followed by a peristaltic wave. The constriction is preceded by a bulging which is more marked than the former. The degree of the constriction (and bulging) is variable. Weaker waves sometimes do not finish the course. A complete course of a wave in one direction lasts from thirty to fifty seconds. The average rate of the movements is about one per minute, but the rhythm is far from being regular.

Some influences suppress cecal peristalsis. Ether applied through the nose stops the movements but they return in about a minute after the ether is removed. Pain, struggle and fright stop the movements; but they soon return again. The most striking effect, however, is the one caused by opening the abdomen: the peristaltic movements as a rule disappear completely and permanently.

What is the cause of this complete abolition of the movements? We thought it might be due to the strong and perhaps continued pain which the laparotomy causes, and tested this theory in the following way. The dorsal cord of a rabbit which showed well defined peristalsis of the cecum was cut at about the third vertebra. As a rule, in such experiments, the peristalsis was stopped for an hour and longer. After the peristalsis had been completely reestablished the abdomen was opened. The laparotomy could now cause no pain; nevertheless it completely abolished the peristalsis, as in a normal animal.

In the course of the latter series of experiments we made the observation that it was not necessary to open the peritoneal cavity to inhibit the movements. Cutting through the skin in the linea alba (in an animal with a cut cord) and dissecting it extensively from the muscles below was sufficient to abolish all cecal peristalsis. Furthermore, the movements returned as soon as the muscles were again covered by the skin, the cut edges of which were held together by clamps. It looked as if the cooling and drying due to the impact of the air upon the muscles above the cecum might have caused the suppression of the movements. But suspending the skin flaps and filling up the cavity above the muscles with warm physiological salt solution did not restore the cecal peristalsis. Furthermore extensive dissection of the skin of the lower

extremities also suppressed these movements. Finally immersion of the lower half of the animal in a warm saline bath inhibited the movements for twenty minutes and longer. When the peristalsis was reestablished it could then again be inhibited by taking the animal from the bath. All the various conditions referred to could affect the cecum only reflexly and not directly.

These experiments led to the inevitable conclusion that the warm or cool bath, and the dissections of the skin over the abdomen and the lower extremities, were various forms of more or less effective stimuli which caused reflex inhibition of the cecal movements. The path of these reflexes could run only through the dorsal cord below the cut. This conclusion was then tested by the effect which the complete destruction of that part of the cord would have upon the inhibitory reflexes. Cecal peristalsis is frequently abolished by such an operation, but reappears sooner or later, and then is often more marked than before the destruction. It was found that after the destruction of the cord the peristalsis of the cecum could not be inhibited by baths, dissections, etc. It was thus established that the cecum is under the control of inhibitory influences invested in the cord, which can be called into action by various peripheral stimulations. Such a stimulus is also exposure to the air of a part of the body which is usually more or less covered.

Under these circumstances we had reason to assume that the inhibitory influence of a laparotomy might be due also to such a stimulation and that it is in the nature of a reflex inhibition. But after further experimenting we found that opening of the abdomen, whether within a saline bath or not, unlike the other peripheral stimulations, inhibits greatly the cecal peristalsis : even after the destruction of the cord, only a few incomplete cecal waves appear after a laparotomy. We must then conclude that direct stimulation of the cecum caused by its exposure to abnormal conditions is capable of inhibiting its movements also directly. Laparotomy therefore abolishes the movements of the cecum by direct inhibition assisted probably also by reflex inhibition.

As to the cause of the movements of the cecum we found that the peristalsis ceased after cutting both vagi. Furthermore stimulation of the peripheral end of one vagus causes a tetanic contraction of the entire cecum, especially after destruction of the cord.

The latter effect is quite peculiar, however. The tetanus lasts only a short time, no matter how long or brief the stimulation may be. Moreover, the effect cannot be obtained by a second stimulation unless quite a long interval passes between the stimuli.

(Some of the above mentioned facts were demonstrated on an animal with destroyed cord.)

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Deglutition through an esophagus partly deprived of its muscularis, with demonstration.

By **S. J. MELTZER.**

[*From the Rockefeller Institute for Medical Research.*]

As a result of the experiments which Kronecker and I carried out about twenty-seven years ago, it appeared to be conclusively established that liquids are squirted down into the esophagus by the force of the contractions of the mylohyoid muscles and some muscles of the tongue, and that liquid thus projected reaches the cardia long before the arrival of the peristaltic wave. At that time the experiments were carried out on a human esophagus. About ten years ago in a series of experiments on the dog I found that our contention held good also for that animal. Cannon and Moser, however, who studied the esophagus by the fluoroscopic method, although confirming our conclusions for the human being, state that "in the dog and cat but little variation was seen in the swallowing of liquids and solids." Recently Schreiber stated that even in the human being, liquids, just like solids, are not squirted down but are carried by the muscles of the mouth and tongue to the pharynx, whence they are conveyed further into the esophagus by the contractions of the constrictors of the pharynx and are finally transported into the stomach by the peristaltic movements of the esophagus. In other words, liquids are also slowly pushed forward through every section of the path of deglutition by the contraction of the muscle fibers of that section; there is no part of that long path through which liquids are thrown or squirted.

I do not intend to enter into an analysis of the experiments and arguments upon which Schreiber founded his views. The object of

my communication was to demonstrate *a dog drinking in a perfectly normal manner, although a large section of its path of deglutition was deprived of all muscle fibers.* In a number of dogs I have completely removed the muscularis from the entire cervical esophagus. Already on the next day after the operation they drank milk and water like normal dogs. In these cases there were no muscle fibers for quite a long distance to do the slow work of pushing the liquids into the thoracic esophagus. They were apparently squirted through the cervical esophagus by a muscular force located anteriorly to the esophagus. That this force is not due to the constrictors of the pharynx was demonstrated by another experiment. In one dog, besides the removal of the esophageal muscularis, the middle and lower constrictors of the pharynx were cut and completely put out of function. This dog, also, drank without any difficulty the day after the operation. The throwing force is apparently exercised by the muscles of the mouth and tongue.

I wish to call attention to another point. Recently again it was claimed that liquids go down the esophagus by the force of gravity. No experiments were offered in proof of that contention but it had the support of the authority of Von Mickulicz. In my demonstration the bowl of milk was placed on the floor and the large dogs that had been operated on drank from it against gravity without any difficulty.

I would call attention to another matter which has been overlooked by some writers. We have established the fact, and it is easily demonstrated, that each act of swallowing inhibits the peristalsis relating to the preceding deglutition, and when swallows follow one another at intervals of one second there is no peristalsis in the esophagus until after the last swallow. Dogs drink very rapidly, and can take 200 c.c. and more without stopping. Where then is the peristalsis even in normal dogs to carry down such a large quantity of liquid? Does the latter simply accumulate in the pharynx and the upper part of the esophagus until the last swallow?

Finally I wish to say that the essential part of our problem is the *establishment of the theory as it was originated by Kronecker, viz., that besides the slow transportation of food by peristalsis, the function of deglutition is provided with a mechanism for a rapid squirting down of appropriate materials.* As to which of the mechanisms

comes into play in any specific case depends upon the nature of the material which is swallowed. We said that *liquid* is squirted down, but I am quite sure that thick syrup is not squirted farther than the upper part of the esophagus, if so far. We said that semi-liquids or semi-solids are also thrown down. We came to this conclusion from observations made on the swallowing of bread thoroughly softened in water. Possibly in this case a separation took place and the water was thrown down while the bread or some of it stuck to the wall of the gullet and was later gathered up by the peristalsis. It is not improbable that this is what occurs when a mixture of bismuth and water is swallowed. The water may be squirted down, while a large part of the bismuth may stick to the wall and be gathered up later by the succeeding peristalsis — and it is the latter which is probably seen through the fluoroscope.

32 (175)

Immunity against trypanosomes.

By **F. G. NOVY.**

[*From the Hygienic Laboratory of the University of Michigan.*]

It is an established fact that rats which have recovered from an infection with *Tr. Lewisi* are immune to subsequent inoculation with that species of flagellate. The same holds true for cattle, sheep, goats, etc., that have recovered from the infection caused by the pathogenic trypanosomes, such as nagana, surra and dourine. This condition of active immunity is seemingly possible only in those species of animals that are relatively insusceptible, for with really susceptible species the infection is always fatal.

Heretofore all experiments on artificial immunity against trypanosomes have been made on animals that have recovered from the effects of the parasite which has been living and multiplying in the blood-vessels of that animal. Now that cultures of some of these organisms, as for example *Tr. Lewisi* of the rat and *Tr. brucei* of nagana, are possible it was desirable to ascertain whether or not they could be used to immunize against the virulent organisms. It may be said, in passing, that cultures of both of these trypanosomes, even after they have passed through a hundred generations or subcultures in the course of two years, do not be-

come attenuated by such prolonged consecutive passage but readily infect susceptible animals.

We have shown, however, that cultures of *Tr. brucei* can be attenuated by exposure for about two days at 34° C. By repeated injections of cultures thus treated, attempts have been made to immunize rats and guinea-pigs against *Tr. brucei* but thus far these have been but partially successful. That is to say, there has been at most a survival for a few days of the treated as compared with the untreated animals. The failure to immunize with such cultures is attributable in part to the excessive susceptibility, of the animals employed, to infection with *Tr. brucei*, and in part to the existence of a negative phase following the injections. It is desirable to repeat these experiments with less susceptible animals.

In view of the fact that rats invariably recover, some soon, others late, from infection with *Tr. Lewisi*, and the further fact that rich cultures of this organism are readily obtainable, it is evident that this species is well adapted for studies on immunity. Up to the present time it has not been satisfactorily shown that trypanosomes elaborate toxins or that they confer immunity by means of soluble or intracellular products. The latter problem was approached by means of plasmolyzed cultures. To effect solution of the trypanosomal cells the cultures were taken up in distilled water and dialyzed in collodium sacs. Usually after one or two hours of such dialysis in distilled water the trypanosomes completely disappear and the intracellular matter apparently passes into solution. By means of such cultures it has been shown that rats which receive three or more injections on alternate days, on subsequent inoculation with a minimal infective dose of fresh trypanosomal blood from a rat, do not become infected, whereas controls are positive. With such solutions it is possible to hyperimmunize rats so that 0.5 c.c. of the immune rat blood protects against a simultaneous and separate injection of the infective blood.

Protection is seemingly obtained against *Tr. Lewisi* by simultaneous and separate injection of the infective blood and plasmolyzed culture, followed 24 hours later by a second injection of the latter. Repeated injections of too large a quantity of the plasmolyzed culture and at too short an interval leads to a negative phase, the presence of which is indicated by the unusually early appearance of trypanosomes in the blood after inoculation with the virus.

Inasmuch as it may be said that the plasmolyzed material does not represent a true solution, a series of experiments were made with the filtered (Berkefeld) plasmolyzed liquid. While these experiments go to show that immunity can probably be induced by such filtered soluble products, they are not as decisive as they should be and for that reason will have to be repeated. The chief reason for this uncertain result is the rather frequent failure of the control rats to develop infection. Although young rats (50–80 grams) were used to guard against previous infection with trypanosomes, it is certain that a large percentage of the rats, as purchased on the market, have acquired an immunity against *Tr. Lewisi*. That the immunity encountered is really acquired and not natural is shown by the fact that we have many times isolated *Tr. Lewisi*, by means of the cultivation method, from rats which on repeated examination were found to be free from parasites and hence were supposed to be normal.

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On secondary transplantation of a sarcoma of the rat.

By **SIMON FLEXNER** and **J. W. JOBLING.**

[*From the Rockefeller Institute for Medical Research.*]

At a meeting of the Society held on October 17, 1906, we presented specimens of a sarcoma of the rat which was being transplanted successfully.[1] In the course of the transplantations the percentage of successful issues has reached approximately one hundred. In many series, every transplanted fragment developed into a tumor, and in none of the latter series has the percentage of "takes" fallen below ninety. The tumor having reached this maximum of infectivity, it was thought desirable to ascertain to what extent secondary transplantation would succeed. The method followed was to inoculate rats, in which a tumor nodule was already present, with another fragment of the tumor tissue. The second inoculation was made, as a rule, on the side of the body opposite the existing nodule, but in a few cases it was made in the tissues adjacent to the first nodule. After the second growth had developed to the size of a pea or bean, the rats were

[1] This volume, p. 12.

killed in order to determine whether metastasis from the first inoculation had taken place. The results of this series of experiments show that secondary inoculation succeeds in a high percentage of the rats in which no visible metastases can be seen, and in which visible metastases, in the lungs chiefly, are present. The exact figures will be given in the complete publication to be issued soon.

The results of this series of experiments bear upon the view expressed by Sticker, that a primary tumor protects the body from the development of a secondary tumor until the period of metastasis arrives, and upon Ehrlich's negative results in secondary transplantations of a rapidly growing mouse carcinoma. The sarcoma of our experiments is characterized by its infiltrative growth, but it increases far less rapidly than the most active of Ehrlich's tumors, and reaches, in relation to the size of the rat, no such large size as the latter does in proportion to the size of the mouse.

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On certain chemical complementary substances.

By HIDEYO NOGUCHI.

[*From the Rockefeller Institute for Medical Research.*]

In blood serum there is a constituent known as complement or alexin, which dissolves blood corpuscles or bacteria when the latter are properly sensitized. Its existence can only be demonstrated by the aid of immune bodies or amboceptors. The action of complement disappears when the serum gets old or is heated to 56° C. for a short time. The fate of complement after inactivation is not known. Complement is generally believed to undergo disintegration. Blood serum yields upon warm alcoholic extraction a substance or a group of substances of powerful lytic activity. The same is also true of leucocytes, glands and certain visceral organs. On account of some differences existing in the lytic mechanism and thermal resistance between genuine serum complement and alcoholic "extract lysins," no direct comparison has been made to establish a possible relationship between these two constituents. Complement is lytic only in the presence of immune

bodies, while the extract lysins are active by themselves. The action of complement diminishes with age and is destroyed by a temperature of about 56° C., whereas the extract lysins do not deteriorate with age or on boiling. So the general conception of today is that they are entirely distinct classes of bodies. Up to the present, no account of the parts which may be played by the other serum components has been taken into consideration. A comparison made under different conditions is devoid of value, and observations on this point seem desirable. I have therefore subjected both complement and the "extract lysins" to a comparative study under the same conditions. I have also identified the chemical nature of various "extract lysins," and pure chemical preparations have been subjected to a similar comparative study. My method of obtaining lytic substances from the blood or other organs was carried out as follows:

To one volume of blood or thick emulsion of any organ, three volumes of 95 per cent. alcohol are added. The mixture is left for about a week at 45 or 50° C. Then the filtrate is evaporated to dryness. The dried mass is extracted with hot alcohol. The alcoholic extract is dried. The dried mass is extracted with ether. The ether insoluble fraction is usually highly lytic, while the other fractions are inactive. The last, ether insoluble, hot alcohol soluble fraction is, of course, free from salts, proteins, neutral fats, fatty acids, cholesterin and its esters, lecithin and other phosphorized fats. It is soluble in water or 0.9 per cent. saline solution with slight opalescent appearance, and is neutral to litmus. Chemically, this fraction represents various soaps. The addition of acetate of lead and subsequent ethereal extraction removes its original lytic substance. Any strong acid produces a milky appearance due to the splitting of the soapy substance, and its hemolytic activity is reduced. Osmic acid gradually turns the solution dark. The solution yields a thick precipitate with phosphotungstic acid and with bromine. Millon's test is negative. This fraction, therefore, consists of various soluble soaps derived from the blood and organs.

My experiments with various soap fractions of the blood and organs show that such fractions possess considerable lytic activity when employed in 0.9 per cent. saline solution. The corpuscles

used were always washed free from the serum, as the latter paralyzes the lytic action of the soap fraction. It was found that the addition of an adequate quantity of indifferent or non-specific serum to the extract removed the lytic property of this fraction. But this inactivation was again found to be only superficial, for the extract was not inactive upon the corpuscles which had been treated with specific or normal amboceptors, nor was it inert in the presence of suitable immune bodies. In other words, this soap fraction acquires the property of acting as a complement. This artificial complement can easily be inactivated by heating it to 56° C. for half an hour, or by leaving it for a week or longer at room temperature. Its complementary action is absent at 0° C. Like serum complement, it becomes inactive when mixed with adequate quantities of various alkali earth salts of strong acids, and any acid stronger than carbonic acid. Alkalies delay the complementary action of this mixture. It may be stated here that the soap fraction in a protein-free solution cannot be inactivated by acids or alkalies. Without the serum proteins, no inactivation at 56° C. or on account of age or by suppression of its action at 0° C. can be obtained. All these characteristics of a complement are possibly to be ascribed to the serum proteins which are present.

My experiments with pure preparations of various soaps not only strengthen the above findings, but they further furnish explanation of the inactivation processes of various alkali earth salts upon complement and the soap fraction of the blood or organs. In this series of experiments, I have employed stearates of sodium, magnesium, calcium and barium, and oleates of ammonium, neurin, sodium, magnesium, calcium and barium. With the exception of certain alkali earth soaps, they are soluble with opalescence in 0.9 per cent. saline solution. Oleate soaps are, as a rule, more easily soluble than the corresponding stearates. As regards their hemolytic activity, it may be stated that the oleates are nearly as much as ten times more powerful than the stearates, and that all insoluble soaps are without lytic action. Of the oleates, neurin soap is the most soluble, and ammonium soap the least. These soluble oleate soaps were used in 1/100 to 1/200 N solutions. 0.5 c.c. of 0.1 per cent. solution (ca. 1/300 N) of these soaps added to 2 c.c. will effect complete solution of a 5 per cent. suspension of ox corpuscles.

Like the soap fraction of blood or organs, all these soaps become inactive when mixed with a certain amount of serum. This inactivation is again an apparent one, because the presence of suitable immune bodies hinders the paralyzing action of the serum to a great extent, or such mixture may be inactive upon normal corpuscles, but active upon those which have been sensitized properly. This complementary action of the mixture of soap and serum is absent at 0° C. and disappears at 56° C., or with age. Chlorides, sulphates or acetates of calcium or barium inactivate the mixture, just as in the case of serum complement or "extract complements." This inactivation cannot be anything more than the formation of the insoluble, inactive soaps. The action of various acids and alkalies is exactly the same as in the cases of complement and "extract complements."

In this place I must not omit reference to certain interesting phenomena which I met with during the experiments on soaps as venom activators. As we have shown elsewhere, venom is inactive without the aid of a second substance. We found that this second substance can be the complement of serum. Kyes discovered later that lecithin is activating for venom, and thinks this is the only class of bodies which is responsible for venom hemolysis. Complement has been placed in a doubtful position as a venom activator. My present work, however, again upholds our previous view that complement is a very important venom activator of serum. Certain fresh serums contain venom activator. If we add to such serums certain amounts of calcium chloride, their activating property is easily destroyed. Complement also disappears in these instances. But if we heat the inactivated serums to 75° C. or higher, then they acquire a new, powerful, venom activating property, which cannot be removed by calcium chloride. On the other hand, ox serum contains almost no venom activator in the fresh state, but acquires one when heated to 75° C. or higher, and this acquired activator cannot be inactivated by calcium chloride. If we take two tubes of fresh ox serum and add soap to one and lecithin to the other, we get venom hemolysis in both tubes. But if, before we add venom, we introduce a certain amount of calcium chloride into each tube, and then venom, venom hemolysis will occur in the tube with lecithin, but not in the tube with soap. It would be

very interesting to ascertain to what extent lecithin is concerned in venom lysis caused by fresh serum.

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Effects of experimental injuries of the pancreas.

By **ISAAC LEVIN.**

[*From the Department of Pathology of Columbia University, at the College of Physicians and Surgeons.*]

A review of the experimental work done so far shows clearly that injuries of the pancreas produce different effects on the organism than the complete removal of the organ. After the latter operation the animal succumbs with the symptoms of subacute diabetes, but a comparatively slight injury to the organ may kill it within twenty-four hours, producing an entirely different symptom complex.

It seems very difficult to form a correct idea of the etiological relation between a certain injury to the pancreas and the disease process that so rapidly kills the animal, because in all the experimental work thus far reported, an injury which results fatally in a certain number of animals, produces no effects on others.

Doberauer reported (in *Centralbl. für Chir.*, Nr. 28, 1906) a series of twenty-one experiments on dogs. In each case he doubly ligated and severed the pancreas with identical results in all the experiments, viz., the development of fat necrosis, sub-serous peritoneal hemorrhages and free hemorrhagic fluid in the peritoneum. The animals were either dead or moribund within twenty-four hours. The author ascribes the fatal results in his experiments to a combination of stasis of secretion, some abnormality in the circulation and a lesion of the parenchyma of the pancreas. The experiments of Doberauer differ from all previous investigations in the fact that he obtained the same results in every experiment. It seemed advisable to repeat his experiments, because, if found correct, they could subsequently be varied so as to afford a clearer insight into the etiological moment of the injury which produced the acute fatal disease of the animal.

The operation of Doberauer was first repeated in exactly the

same manner on six dogs. Of these animals only one died in twenty-four hours. The autopsy showed congestion of the pancreas near the ligatures (otherwise the organ was macroscopically normal), sero-fibrous peritonitis and no fat necrosis. The other animals remained healthy, and when subsequently killed, showed nothing abnormal at autopsy. Thus the results in this first series of experiments did not seem to coincide with those of Doberauer. It remained to be seen whether better results could not be obtained by varying the experiments to some extent. A priori it seems certain that the deleterious effect of the injured pancreas on the organism is due to a change either in the secretion of the organ or in its circulation or in the parenchyma, or in a combination of the three. In the first series of experiments the result was mostly a stasis of secretion.

In the second series undertaken on four dogs, a part of the pancreas about an inch long was crushed with an artery forceps in the middle of the gland and every bleeding vessel ligated separately. In this way some of the parenchyma of the organ was injured and instead of producing a stasis of the secretion, it was given a free exit in the peritoneum. All four animals remained normal.

In the third series of experiments the pancreas was either doubly ligated or part of it crushed and, besides, the most important veins leading from the pancreas were ligated. In this operation a hemostasis was added to the results produced in the previous experiments. The operation was performed on six dogs. Three dogs died in from twenty-four to forty-eight hours. The autopsy showed acute pancreatitis with fat necrosis. The other three dogs remained apparently healthy, but when killed subsequently showed at autopsy a condition of interstitial pancreatitis. These investigations are not yet near completion, but so far as can be judged from the material on hand, those injuries produce the gravest effect on the organism which cause the most serious interference with the circulation of the pancreas. To produce a fatal disease it does not suffice to interfere partly with the free secretion of the pancreatic juice into the intestines as in the first series of experiments, or to injure some of the parenchyma and at the same time allow the juice to secrete into the peritoneal cavity, as in the second series.

The interference with the circulation must be such as to produce a lesion of the whole organ so that not only will the organism be deprived of the normal function of the pancreatic cells, as after extirpation of the organ, but also every cell will become diseased and begin to act abnormally and injuriously to the organism.

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The pathology of function; an experimental laboratory course.

By **HAVEN EMERSON.**

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

To fill the gap between physiology and histology on the one hand and pathology as usually taught upon the other, the following experimental procedures were given in a three weeks course on some common disorders of function and the physiological methods of detecting them and treating them.

1. Peripheral arterial blood pressure in man varied by the following procedures:
   - During digestion.
   - Variations of position.
   - Attempted defecation.
   - Adrenalin administration.
   - Amyl nitrite administration.
   - Faradic stimulation of nares.
   - Inhalation of ammonia.
   - Exercise.
   - Hyperpnea.
   - Administration of coffee.
2. Pericardial effusion imitated by saline solution introduced into the pericardial sac.

   Myocardial changes produced by injecting alcohol into the heart muscle.
3. Aortic stenosis.
4. Aortic regurgitation.
5. Pleural effusion.

6. Extremely high vascular pressure causing acute cardiac dilatation resulting in pulmonary edema, produced in a mammal by large doses of adrenalin.
7. Pneumothorax.
   Hydro-pneumothorax.
   Pneumo-peritoneum.
   } Their physical signs and their effects upon blood pressure, heart action and respiration.
8. Pneumo-peritoneum.
   Hydro-peritoneum.
   Gastro-intestinal distension with air.
   } Studied in detail, as indicated for No. 7.
9. Heat, cold and hemorrhage in their relation to respiration, circulation and the etiology and treatment of "shock."
10. Intracranial pressure and the results of its increase upon respiration and general blood pressure.
11. Acute bronchitis, produced by the administration of chlorine gas as an irritant in the inspired air.
12. Heat, cold and counter-irritation in their relation to temperature and circulation in the superficial and deeper portions of the body.
13. Renal secretion and general blood-pressure as affected by
    Amyl nitrite,
    Adrenalin,
    Heat,
    Cold,
    Vagus stimulation.
14. Capillary circulation as affected by pressure locally and vasoconstriction generally.
15. Mitral stenosis.
16. Secretion of bile as affected by changes in blood pressure and the use of cholagogues.

37 (180)

The influence of alcohol on the composition of urine.

By **F. C. HINKEL** and **WILLIAM SALANT**.

[*From the Laboratory of Biological Chemistry of Columbia University, at the College of Physicians and Surgeons.*]

About twenty years ago Schumoff and Simanowski showed that oxidation in the body is markedly diminished after the

administration of alcohol. They estimated oxidation in the body by the amount of phenol found in the urine after giving benzol. By this method they obtained results which showed that the oxidative processes in the body decreased 60–75 per cent. as a result of administering alcohol. Their findings seemed to be confirmed later by Presnyakoff who studied this problem in a different manner. He determined the amount of neutral sulphur before, during and after the administration of alcohol and concluded that the amount of unoxidized sulphur decreases during the alcohol period. As his data, hardly justify such a conclusion, we decided to reinvestigate the subject, with special reference to the amount of unoxidized sulphur as affected by alcohol. In the course of the research, however, it seemed to us desirable to study exactly also the effects of alcohol on the other urinary constituents. We carried out our experiments on a healthy dog kept in one of the improved metabolism cages devised and described by Professor Gies.

The diet consisted of meat, cracker meal, lard, and bone ash, given with definite amounts of water. Each experiment was begun after the dog reached a constant weight. During the control period 50 c.c. of water were given daily by mouth through a stomach tube for 6 days. During the next 6 days 50 c.c. of alcohol were administered in the same way. This was followed by another alcohol period of 7 days, when the same daily volume of 70 per cent. alcohol was given. The alcohol was then discontinued and water was given again for 10 days in the same way as in the control period. Samples of forty-eight hour urine were taken for analysis. The results of our observations on one dog show that the neutral sulphur of the urine increased 12.68 per cent., when 50 per cent. alcohol was given. When the same amount of 70 per cent. alcohol was given the neutral sulphur increased 52.88 per cent. as compared with that of the control period. The amounts of neutral sulphur were as follows : Control period — 27.2 per cent. First alcohol period, when 50 c.c. of alcohol were given, the amount of neutral sulphur was 40.5 per cent. of the total sulphur. During the third period, when 70 per cent. of alcohol was given, the amount of neutral sulphur constituted nearly one half of the total sulphur — 47 per cent. The total sulphur of the

urine showed marked diminution during the first alcohol period, when the average daily output was 255.3 mgs. as against 336.8 mgs. in the control period, which is a diminution of 24.2 per cent. When the same volume of 70 per cent. alcohol was administered, however, the difference was less marked, the daily average being 297.8 mgs. of sulphur or 11.4 per cent. less than in the control period.

The inorganic and ethereal sulphates of the urines were likewise determined. The former showed a striking diminution during the alcohol periods. When 50 per cent. alcohol was given the daily average output of inorganic sulphates was 133.4 mgs., while the amount eliminated per day during the control period was 208.1 mgs. — a diminution of 36 per cent. With 70 per cent. alcohol the average amount per day was 69.2 per cent. During the after period, when alcohol was discontinued, the inorganic sulphates rapidly returned to the normal. The amount found in the combined urines of the 3d and 4th days was about the same as in the control period. In the subsequent days the sulphates steadily increased in amount until on the 9th and 10th days the output was even slightly greater than in the control period. The ethereal sulphates in the urine of this dog presented very interesting results. There was considerable fluctuation in the amounts found in the control period. The amount excreted during the first 2 days was 69.1 mgs.; 3d and 4th days — 48.6 mgs.; 5th and 6th days — 104.4 mgs. During the first alcohol period, the variation was much less; the quantity eliminated was also markedly diminished. The diminution continued all through the second alcohol period, as well as in the after period when alcohol was discontinued. The ratio of the simple sulphates to the ethereal sulphates rose in the alcohol period but was highest in the after period.

The elimination of phosphoric acid likewise showed considerable diminution in the alcohol periods. While the average amount of P_2O_5 excreted during the control period was 801 mgs. per day, in the first alcohol period it was 552 mgs. — a diminution of 40 per cent., which practically continued when 70 per cent. alcohol was given. In the after period a decided tendency to return to the normal was noticed but at the end of the 10 days, the amount excreted was 13–15 per cent. below that of the control period.

The urinary nitrogen likewise showed a considerable diminution when 50 per cent. alcohol was administered. The total nitrogen decreased 12 per cent. When the quantity of alcohol was increased, however, the nitrogen failed to undergo a corresponding diminution — our analysis showed a decrease of only about 4.4 per cent. as compared with the control period. The average daily output of nitrogen remained practically the same during the 10 days of the after period. We have also made determinations of the urinary chlorides. The influence of alcohol was plainly evident and was similar to that on the other urinary constituents. The chlorides decreased 17–22 per cent. but they practically returned to normal in the after period which was continued for 10 days.

As was mentioned before, these particular results were obtained in the analysis of the urine of one dog. Whether alcohol behaves the same in other individuals remains to be seen. There are some indications, however, that not all dogs react alike to alcohol.

Table showing the influence of alcohol on the composition of dog urine. Average daily output in grams.

		Alcohol period.		
	Fore period.	50 per cent.	70 per cent.	After period.
Total nitrogen	5.5856	4.9066	5.2846	5.259
Total sulphur	0.3368	0.2553	0.2978	——
Neutral sulphur	0.0917	0.1035	0.1402	——
Inorganic sulphur	0.2081	0.1334	0.1442	0.2187
Ethereal sulphur	0.0371	0.0185	0.0133	0.0067
P_2O_5	0.8016	0.5526	0.5730	0.6959
Chlorides	0.3872	0.3000	0.3210	0.3631

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Spirochæta microgyrata (Löw) and mouse tumors.

By GARY N. CALKINS.

[*From the Department of Zoology, Columbia University.*]

A black female mouse purchased from a breeder in New York City and belonging to a set of from 200 to 300 mice under observation by Mr. Horton of Columbia, in experiments on Mendelian inheritance, developed a tumor on the right fore leg. The shoulder and axilla were involved and the mouse could not use the leg in

walking. At one point the hair had been scratched off and the skin bared but the tumor was not ulcerated. On removing, there was no evidence of hemorrhage and a solid tumor about the size of a hickory nut and weighing about 4 grams was taken out. It had become attached to the skin but was apparently not attached elsewhere. A piece of the tumor weighing about 1½ gram was ground up with normal salt solution (3 c.c. normal salt to 1 gram of tumor material) and this was injected under the skin of the neck in twelve white mice. The remainder was fixed in 10 per cent. formalin and in Zenker's fluid. No tumor has yet appeared in the inoculated mice.

Dr. Ewing described the tumor from sections as an adenoma with glandular characters of the thyroid. Necrotic areas are few in number and very small; mitotic figures are rare.

Sections of the tumor put through the Levaditi silver nitrate method reveal the presence of *Spirochæta microgyrata*. The spirochæte is not widely distributed but may be found at various points in the tumor mass, especially in the few small vacuolar areas. It has the characters of the species described by Löwenthal in 1905 in a case of human ulcerated carcinoma. It varies in length from three to eight microns and has from four to thirteen turns or "nodes," the average length of a node being six tenths of a micron. The undulations are steep and closely pressed as indicated by the specific name *microgyrata*. In view of certain minor differences in staining power and habitat, I have given this organism a new variety name.[1]

This is the tenth primary mouse tumor in which *Spirochæta microgyrata* has been observed. The first in which it was described was a tumor in a mouse from Granby, Mass. In that tumor the spirochætes were much more numerous than in the tumor now described; the necrotic areas of the former tumor mass were more extensive and much more numerous than in our tumor and it had more of the characteristics of carcinoma than ours.

In all primary tumors the spirochætes are much less numerous than in the transplanted tumors of the Jensen series. In the latter, especially in those strains giving a yield of 80 per cent. to 90 per cent. on inoculation, the tissues are fairly riddled with these spiro-

[1] See *Journ. of Inf. Diseases*, March, 1907.

chætes; while every mouse tumor that has been put through the Levaditi method shows the presence of these organisms.

Neither Löwenthal, nor Gaylord, nor I have claimed that these spirochætes are the cause of mouse tumors, nor have we claimed that spirochætes are the cause of human carcinoma. We have always held to the parasite theory of cancer, however, and the thus far invariable presence of *Spirochæta microgyrata* certainly gives us no reason to change our position. In view of the small number of spirochætes present, it may be pointed out as significant that of the thirty-seven primary tumors with which we have dealt, only two have been transplantable.

39 (182)

On the competency of the venous valves and the venous flow in relation to changes in intra-abdominal pressure.

By **RUSSELL BURTON-OPITZ.**

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

In the present series of experiments performed upon dogs, the blood flow in the femoral vein was measured by means of the recording stromuhr, described by the author.[1]

During the experiment the intra-abdominal pressure was suddenly raised either by pressure with the hands upon the external surface of the abdomen, or by inflation of the cavity with air.

In both cases a retardation of the venous inflow was noticed, the degree of the slowing of the blood stream being in accordance with the increase in the intra-abdominal pressure. Thus, in one specific instance the intra-abdominal pressure was raised to 70 mm. Hg. The venous pressure increased accordingly from 4.5 mm. to 64.0 mm. Hg, while the blood flow decreased from 1.02 c.c. to 0.08 c.c. per second.

A similar retardation occurred also with the chest widely opened. Raising the intra-abdominal pressure produced no marked influence upon the flow in the external jugular vein.

A more abrupt and decisive slowing of the blood stream occurred, when pressure was exerted with the hands. It then became possible at times to produce not only a stoppage of the

[1] This volume, p. 24.

flow, but also a slight backward movement, such as can be accounted for by the stretching of the venous valves.

40 (183)

On vaso-motor nerves in the pulmonary circuit.

By **RUSSELL BURTON-OPITZ.**

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

To test the existence of vaso-motor nerves in the pulmonary circuit, the following method was devised: The inlet tube of the stromuhr, recently exhibited by the author before this society,[1] was connected with a receptacle containing Ringer's solution and the outlet tube with a button cannula, to be inserted subsequently into the pulmonary artery of dogs. The chest wall having been resected, loose ligatures were placed around the nerves in the vicinity of the ganglion stellatum and the pulmonary artery. A cannula was inserted into the appendix of the left auricle.

The procedure was as follows: Long forceps-clamps were quickly placed upon the central portion of the pulmonary artery, and transversely across the left auricle close to its junction with the left ventricle. The button cannula having been inserted into the pulmonary artery distally to the clamp, the blood-vessels of the lungs were then supplied with circulating fluid from the receptacle and drained by way of the cannula in the left auricle. Thus, all influences of the heart which might have disturbed vaso-motor reactions in the pulmonary circuit were excluded.

A change in the flow directly attributable to vaso-motor influences, could not be obtained by stimulation of any of the aforesaid nerves. Stimulation of the vagus in the neck, as well as centrally and distally to the ganglion stellatum, was ineffective.

In view of these negative results, it seemed advisable to test the influence of adrenalin upon the flow through the pulmonary blood-vessels. A T-tube was inserted between the stromuhr and the button cannula, through which solutions of different strengths were injected. In spite of the fact that these solutions had pro-

[1] This volume, p. 24.

duced decided vaso-motor reactions in other parts of the body a few minutes previous to these experiments, they remained ineffective when introduced into the pulmonary circuit.

41 (184)

The effect of salicylic acid upon autolysis.

By **L. B. STOOKEY.**

[*From the Physiological Laboratory, Medical Department, University of Southern California.*]

The liver, kidney, spleen and muscle taken from dogs which had received subcutaneously doses of sodium salicylate (0.1 gram, in 1 per cent. solution, per kilo of body weight) daily, during a period of ten days, showed rates of autolysis greater than those observed in the same organs taken from normal dogs.

The influence of other drugs upon autolysis is being investigated.

42 (185)

On the synthesis of protein through the action of trypsin.

By **ALONZO ENGLEBERT TAYLOR.**

[*From the Laboratory of Pathology, University of California.*]

The application of the theory of thermodynamics to general chemical reactions has resulted in the definition of the following principles, all of which have been confirmed by experiment as well as by mathematical considerations :

All chemical reactions are reversible reactions ;

All chemical reactions progress to an equilibrium in the system.

There is in every chemical reaction a driving force and an internal chemical resistance.

Catalytic acceleration operates through a reduction in the internal chemical resistance ; since the driving force is unaltered, the station of equilibrium is attained more quickly, that is, the experimental velocity of the reaction is increased.

The catalytic acceleration operates in either direction of the reaction ; no matter in which direction the reaction may happen

to be proceeding at a particular moment, the catalyser accelerates the progress to the station of equilibrium.

On the basis of these considerations van't Hoff ten years ago predicted that the common reactions of fermentation were reversible if the appropriate conditions could be secured. This would mean the synthesis of organic substances through the acceleration of the reversed reactions, and he expressed the suggestion that the syntheses in nature might be regarded as such.

Of the three large groups of organic substances conspicuous in the living plant or animal body, *i. e.*, carbohydrates, fats and proteins, successful reversions have been accomplished in but the first two. Of carbohydrates the following have been synthesized by ferment action : starch, glycogen, cane sugar, maltose, lactose and glucosides. Fats of both the mon-atomic alcohols and of glycerol have been synthesized by ferment action. Two years ago I published the details of a long series of failures at the synthesis of protein. Since that time I have attempted repeatedly to effect the synthesis of the peptids of Fischer through the action of trypsin. The results were entirely negative. Recently Abderhalden has published the negative results of a similiar set of experiments. Not long ago I succeeded in an effort to effect the synthesis of a protein through the action of trypsin. The detailed description of the work, of which this is but a preliminary announcement, will be published in the *Journal of Biological Chemistry*.

Four hundred grams of the protamin sulphate of the striped bass were digested with trypsin until the hydrolysis of the substrate was completed. At the close of the digestion, the solution was miscible with five volumes of acidulated alcohol without the production of any opacity, and gave with cold saturation with sodium chloride no precipitation. This solution was then heated to the boiling point, freed of its sulphuric acid by the addition of barium hydroxid, the excess of barium removed by saturation with carbon dioxide, the mixture filtered hot and filtration repeated until the fluid was clear. This solution then represented a solution of the amino acids, free and combined with carbon dioxide, the products of the hydrolysis of the protamin. The solution was clear, and had an alkaline reaction. This solution was then concentrated until the beginning of precipitation in the cold, from which it was inferred

that the solvent was saturated with the products of the digestion, a theoretically favorable condition for the reversed reaction. To this was then added 300 c.c. of a glycerol extract of livers from large, soft shelled, California clams, which contain a strong tryptic ferment. The solution was then miscible with alcohol without cloudiness. Twenty c.c. of toluol were then added, and the flask, containing over four litres, then sealed and set aside. As time passed this solution became opalescent, then cloudy, and finally a fine white precipitate settled on the bottom of the flask. Five months after the experiment was begun the flask was opened, heated to the boiling point to destroy the ferment, acidulated with sulphuric acid, which dissolved the white precipitate, filtered and then precipitated by the addition of four volumes of absolute alcohol. A heavy, white precipitate was produced, which was collected by filtration, washed with alcohol, redissolved in water, reprecipitated by alcohol, and this procedure repeated four times. The final white powder when fully purified and dried weighed 1.8 gram. Probably one fourth of the amount had been lost in the processes of purification. This powder was soluble in water up to a concentration of about three per cent., was precipitated by acidulated alcohol, and was salted out of a ten per cent. solution of sodium chloride. It was analyzed for carbon, hydrogen, nitrogen, and sulphuric acid. The results of these analyses agree well with the known composition of the protamin sulphate. This for the protamin of the striped bass I long ago determined to be $C_{30}H_{60}N_{17}O_6 \cdot 2H_2SO_4$. Calculated according to this formula, the theoretical percentages and the percentages determined in the analyses were as follows:

	Calculated.	Found.
C	37.85%	37.68%
H	6.72%	6.89%
N	25.13%	24.45%, 24.93%, 25.06%, 25.18%
H_2SO_4	20.60%	20.68%

The conclusion is obvious that the substance formed was protamin.

I had previously carried out experiments with protamin, but always with negative results. The positive result in this experiment must have been due to one of two circumstances. Either to the use of this particular ferment, which is very resistant, or to the use of

the free amino acids and the carbonates, instead of the sulphates, as previously. Future experiments must determine which. A control, a fraction of the original solution without the ferment, has not changed during the time of the experiment. The glycerol extract used, some of which was preserved, is still active; the ferment is therefore very long lived. A culture made of the experimental material at the close of the experiment was negative.

43 (186)

A method for separating leucin from amino-valerianic acid.

By **P. A. LEVENE.**

[*From the Rockefeller Institute for Medical Research.*]

Separation of leucin from amino-valerianic acid was accomplished by means of lead acetate and ammonia. A basic lead salt of leucin, insoluble in hot water, was formed. From a mixture containing 52.53 per cent. of C and 9.39 per cent. of H, by the use of these reagents, a substance was obtained, which had 54.55 per cent. of C and 9.90 per cent. of H. On reprecipitation it acquired the composition: C = 54.70 per cent.; H = 10.09 per cent. Leucin contains 54.89 per cent. of C and 10.01 per cent. of H.

Twenty first meeting.

College of Physicians and Surgeons, Columbia University. March 20, 1907. President Flexner in the chair.

44 (187)

A study of the vital conditions determining the distribution and evolution of snails in Tahiti, with illustrations.

By **H. E. CRAMPTON.**

[*From the Department of Zoology, Columbia University.*]

In presenting the more important results of a recent study in the field of terrestrial pulmonates of the island of Tahiti, belonging to the genus *Partula*, it was shown that different valleys contain forms that, on account of their more or less complete isolation, have come to differ in correlation with their geographical proximity or remoteness. The vital conditions that limit the snails of this island to their particular stations are dryness peripherally, where the valleys debouch upon the coastal alluvial plain, and lower temperature centrally. Only rarely may stragglers pass from one region to another.

Evidence was adduced showing that "mutations" have arisen at various recent times. The observations of Garrett and Mayer, taken in connection with the results of the writer, make it certain that at least three forms have thus originated, at dates that may be determined with substantial accuracy. It was furthermore shown, in corroboration of Mayer's contention, that the environmental conditions cannot be regarded as the factors that have produced the several specific and varietal differentia exhibited by the Tahitian snails.

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The parathyroid gland, with demonstrations of the effects of hypodermic injections of parathyroid nucleoproteid after parathyroidectomy.

By **S. P. BEEBE.**

[*From the Loomis Laboratory, Department of Experimental Pathology, Cornell University Medical College, New York.*]

It has been found that the symptoms of tetany following parathyroidectomy in dogs can be inhibited by the hypodermic injection of parathyroid nucleoproteid. The globulin from these glands has not been found effective. If the nucleoproteid is heated to boiling in an alkaline medium its inhibitive powers are destroyed.

46 (189)

Further experimental and clinical observations on the transfusion of blood.

By **GEORGE W. CRILE.**

[*From the Laboratory of Surgical Physiology, Western Reserve University Medical College.*]

The therapeutic results may be grouped into three classes: positive, negative and undetermined. Among the positive results is transfusion in acute hemorrhage which is apparently final. In pathologic hemorrhage it has proven positive in improving the patient's immediate condition, and in most instances wholly controlled the hemorrhage itself. In shock its value seems far greater than any other remedy hitherto employed by me. From the experimental standpoint it seems to be the most effective treatment of illuminating gas poisoning.

Among the negative results are transfusion in pernicious anemia, leukemia, carcinoma, strychnin poisoning and diphtheria toxemia.

Among the undetermined results may be mentioned chronic suppuration with its attendant debility and anemia, tuberculosis and the acute self-limited diseases.

Of the twenty one clinical cases, all were technically successful.

In every instance the donee experienced a heightened vitality, and in the absence of serious organic disease the patient became buoyant, even jocose. Some had chills during transfusion or soon after, and a majority showed some febrile reaction later.

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A preliminary report on the direct transfusion of blood in animals given excessive doses of diphtheria toxins.

By **GEORGE W. CRILE** and **D. H. DOLLEY.**

[*From the Laboratory of Surgical Physiology, Western Reserve University Medical College.*]

Technique. — The dog was given *subcutaneously* the dose noted. After waiting a certain time an anastomosis was made between one of his vessels (usually, for convenience, the external jugular) and an artery (carotid) of a donor, of equal or usually larger size. When this was perfect, the toxic dog was bled, usually from a femoral artery, as rapidly as possible, to complete exsanguination, and the transfusion was in no case started till cessation of respiration gave warning of the limit's being reached. When this occurred the blood was allowed to flow, under control, until the pulse returned in every case to a better quantity than before. The time taken in transfusing was usually about 15 minutes. (The venous anastomosis was made because more blood went into the donee by it.)

Weight of the donee.[1] kg.	Dose.[2] c.c.	Time of bleeding after dosage. hrs.	Result.[3]
3.13	0.025	24	Died in 84 hours.
4.8	0.025	20	Died in 120 hours.
2.8	0.015	17½	Died in 120 hours.
7.3	0.015	3	Died in 84 hours.
4.5	0.015	1½	Died in 10 days.

[1] Not essential as the donee bled completely and the transfused amount could only be estimated.

[2] The toxin used was a fresh supply (1906). It was not so definite in its effect as regards time as the first. Four control dogs, with 0.015 c.c. each, died in 3, 5, 7 and 8 days respectively; one with 0.02 c.c. died in 3 days and one with 0.025 c.c., in 2 days.

[3] Autopsies were performed on all these dogs, in which the findings were the same as in the controls, *i. e.*, varying degrees of hemorrhagic enteritis, focal hemorrhages in the kidneys and marked cloudy swelling of the liver and kidney, with jaundice. In some, focal necroses of liver and kidney were apparently present. The microscopic part has not yet been worked up.

The experiments were next varied in this way; instead of treating a toxic dog with normal blood, an exsanguinated normal dog was transfused from one which had been given the toxin subcutaneously some time previous, as noted below. To be sure of an excess of toxin the dose was doubled. The technique was the same, under ether with careful asepsis. The vascular anastomosis was made before the normal dog was bled. The time is calculated from when the dose was given till the transfusion was started. In the fourth experiment one donor (St. Bernard dog weighing 40 k.) supplied three small dogs one after another with sufficient blood.

SUMMARY OF EFFECTS ON DONEES.

	Elapsed time between dosage and transfusion.	Dose given donor. c.c.	Result.
1.	6 hours	0.015	Lived 3 weeks under observation; entirely healthy.
2.	4 hours	0.030	Same.
3.	3 hours, 50 minutes	0.030	Same.
4.	*A.* 1 hour, 5 minutes	0.025	Developed paralysis of both hind legs in 10 days.
	B. 3 hours, 10 minutes	0.025	Died in 15 days. Widespread broncho-pneumonia (accidental infection, no other lesion).
	C. 5 hours, 10 minutes	0.025	No ill effects.

No further observations of these dogs were made. The paralyzed dog is certainly suggestive of diphtheritic paralysis. The dog lived for over a month in this paralyzed state, but when he died I was not informed and the body was buried.

INTRAVENOUS INOCULATION.

Elapsed time between dosage and transfusion.	Dose given donor. c.c.	Result.
24 minutes	0.03	Died in 6 days (usual postmortem appearance).

I. SUMMARY OF THE EXPERIMENTS ON THE TREATMENT OF DIPHTHERIC TOXEMIA BY BLEEDING ALONE.

Dose per kg. c.c.[1]	Elapsed time between dosage and bleeding. hrs.	Approximate amount of blood removed.	Result. (In hours after dosage.)
0.015	18	1/3	Died in 36 hours.
0.015	19	1/4	" within 60 "
0.015	7	1/4	" " 45 "
0.015	7	1/5	" " 45 "
0.010	3	1/5	" " 48 "
0.010	3	1/5	" " 100 "

[1] 0.015 c.c. of the toxin per kg. killed control dogs in two days, while 0.01 c.c. averaged somewhat over three days in causing death.

II. BLEEDING FOLLOWED BY IMMEDIATE TRANSFUSION OF SALINE.

Weight of dog. kg.	Dose per kg. c.c.	Amount bled. c.c.	Per cent. of blood removed (approximately).	Elapsed time between dosage and bleeding. hrs.	Result. (In hours after dosage.)
7·3	0.010	200	35	22	Died within 60 hours.
3.6	"	115	50	3½	"
4.8	"	120	33	3	"
4.5	"	110	33	4	"
9.0	"	175	25	3	"

All the inoculations in the last two series were made subcutaneously.

48 (191)

The effect on the normal dog heart of expressed tissue juice from hearts of dogs poisoned with diphtheria toxin.

By **J. J. R. MACLEOD** and **GEORGE W. CRILE.**

[*From the Physiological Laboratory, Western Reserve University.*]

The injection of moderately large doses of diphtheria toxins into animals is followed by no change in arterial blood pressure until after the elapse of a certain latent period, varying from 24 hours in the rabbit to 2–4 days in the dog, when it begins to fall. The fall in blood pressure, having once occurred, rapidly proceeds, so that within a very short time the animal is dead (30 minutes in the rabbit). Both vasomotor paralysis and cardiac failure are responsible for the fall, although it is evident that the cardiac failure is the more important as the immediate cause of death, since mere isolation of the vasomotor center — as after spinal transection — is not followed by such rapid cardiac failure. The vasomotor paralysis of course accelerates the cardiac failure.[1]

Rolly further found that isolation by Hering's method of the heart of a rabbit just dying as a result of diphtheria inoculation and its perfusion with blood from a healthy animal did not in the slightest degree delay the failure.

Although a certain amount of histological change seems always to be present in the myocardium after death from the inoculation of diphtheria toxins, yet it has been considered by Rolly and others as scarcely of sufficient intensity to account for

[1] Rolly: *Archiv für experimentelle Pathologie und Pharmakologie* (1899), xlii; Romberg, Paessler, *et al.*: *Deutsches Archiv für klinische Medizin*, lxiv.

the sudden failure. Furthermore, addition of diphtheria toxins even in very large dosage to the fluid perfused through a Langendorff heart preparation does not influence the beat; nor does its perfusion with the blood of a moribund animal (from diphtheria inoculation).

It has been suggested, therefore, (by Rolly, *et al.*) that the cardiac failure is due to a functional change resulting from the gradual assimilation of toxin by the cardiac muscle until so much had been taken up as to paralyze the muscle. Hence, the long latent period and the rapid course of the failure.

From a consideration of the findings it seemed to us possible that, if any such compound of cardiac muscle substance and toxin were present in the heart, its presence could be revealed by expressing the tissue juices of the heart of a dead or dying dog after inoculation with diphtheria toxins, and then adding this extract to the blood perfused through a normal Langendorff heart preparation. A large Buchner's press was employed by us for preparing such extracts. It was found as a result of the injection of such an extract into the heart that exactly the same result is obtained as when a similar extract of the heart of a normal dog is employed; viz., a sudden and complete inhibition of the beat followed within a minute by marked fibrillation. It was found impossible by any of the numerous methods recommended to remove this latter condition.

A similar result was obtained by injecting a watery solution of the ash of the extracts (made up to the original bulk) so that there can be little doubt that the large amounts of potassium which such an extract contains is responsible for the result. It is, however, somewhat difficult to explain in the same way the marked and persistent fibrillation which occurs, for such is not usually observed after injecting pure solutions of potassium salts. The sudden cessation of circulation alone cannot explain it, else would fibrillation occur in vagus stimulation.[1]

[1] Gross: *Archiv für die gesammte Physiologie* (1903), xcix, p. 264; Braun: *Ibid.* (1904), ciii, p. 476.

49 (192)

Experimental liver necrosis: 1. Hexon bases.

By **HOLMES C. JACKSON** and **RICHARD M. PEARCE.**

[*From the Department of Physiological Chemistry, Bender Laboratory, Albany, N. Y.*]

The following conclusions were reached as the results of the analysis according to the Wakeman-Kossel method for the determination of hexon bases of the normal and necrotic livers of dogs and horses in various stages of necrosis and of the same after autolysis for varying lengths of time.

Necrosis was induced in the case of the dog by means of the injection of hæmotoxic immune sera and in the horses by injections of bacterial toxins.

1. The dry solid content of the (*a*) scattered and of the (*b*) diffusely necrotic liver tissue showed no variation from that of the normal.

2. The nitrogen of the dry substance averaged 11 per cent. in the normal liver, 21.7 per cent. in those with scattered necroses (increase 95.4 per cent.) and 12.65 per cent. in the diffusely necrotic (increase 5.3 per cent.).

3. In the cases of scattered focal necroses the nitrogen precipitable by phosphotungstic acid after acid hydrolysis formed 11.3 per cent. and in the diffused necroses 30 per cent. of the total nitrogen as against 15 per cent. for the normal; a decrease of 25 per cent. for the first and an increase of 100 per cent. for the more advanced type of necrosis.

4. The normal dog's liver apparently possesses no hexon-splitting enzyme, or at any rate the arginase is held in abeyance by factors to be discussed in a later paper, since the nitrogen precipitable by phosphotungstic acid after hydrolysis with acids increased from 15 per cent. to 19.5 per cent. after autolysis for periods varying from 4–8 weeks. This increase (30 per cent.) was about equally divided between arginin and lysin.

5. The necrotic livers allowed to undergo autolysis showed approximately the same percentage loss of phosphotungstic-precipitable nitrogen (hexon) despite the extent of the necrosis.

In the focal necrosis the average was 28 per cent., in the diffuse necrosis 21 per cent.

6. No difference could be observed in the rapidity with which the necrotic liver underwent autolysis, the maximum was apparently reached in four weeks. This phase of the subject will be discussed in a later paper.

50 (193)

The action of nitric acid on the phosphorus of nucleoproteids and paranucleoproteids.

By **A. B. MACALLUM.**

[*From the Physiological Laboratory of the University of Toronto.*]

The manner in which phosphorus is combined in the true nucleoproteids and in those known as the psuedo (para) nucleo-compounds or phospho-proteins has not as yet been definitely ascertained nor has it been determined that the phosphorus in both classes of compounds is similarly or otherwise combined. Burian[1] has, it is true, suggested that in true nucleic acids phosphorus is the bond between the No. 7 nitrogen of the purin bases and the remainder of the nucleic acid molecule, but this view is founded on the fact that the nucleic acids do not give the diazo reaction which he regards as characteristic of those purins in which there is no substitution of the imide hydrogen of nitrogen No. 7 of the purin skeleton, an explanation of the reaction that is rejected by Steudel who has pointed out that thymin gives the diazo reaction of Burian although it does not contain nitrogen in the No. 7 position.[2]

If Burian's suggestion were accepted it would establish a radical distinction between the manner in which phosphorus is held in nucleic acids and that obtaining in paranucleic acids, for in the latter there are no purin bases.

Whether we do or do not accept Burian's view, it is possible on other grounds to establish a distinction between the two classes of compounds in regard to the manner in which the phosphorus is combined in them. For this purpose nitric acid may be allowed

[1] *Ber. d. d. chem. Ges.*, vol. 37, p. 708 (1904).

[2] *Zeit. für physiol. Chem.*, vol. 42, p. 165 (1904).

to act for periods of varying length on pure preparations of the compounds.

In the observations of which the present paper is the result, nucleic acid from yeast and Hammarsten's nucleoproteid of the pancreas were employed as representatives of the true nucleoproteids while caseinogen exemplified the para compounds.

The yeast nucleic acid and the pancreatic nucleoproteid were prepared in such a way as to free them from lecithin and inorganic phosphates. The nucleic acid was dissolved in dilute sodic hydrate solution (1 per cent. strength) and precipitated therefrom with dilute hydrochloric acid. This solution and precipitation was repeated three times. The precipitate was finally extracted with ether in a Soxhlet apparatus to remove all traces of lecithin. The pancreatic nucleoproteid was prepared by extracting the minced pancreas with boiling water, filtering and adding to the filtrate dilute acetic acid, when the nucleoproteid was precipitated. The precipitate was carefully washed with very dilute acetic acid solution, then dissolved in very dilute ammonium hydrate and the solution rendered acid with acetic acid. The precipitate so obtained was again carefully washed, dissolved and once more precipitated. It was then extracted with ether to remove all traces of lecithin.

In order to determine the absence of phosphates portions of the nucleic acid and of the nucleoproteid so obtained were treated with a solution of ammonium molybdate in nitric acid prepared according to Fresenius' method and the addition of the reagent was followed immediately by that of a solution of phenylhydrazin of 2 per cent. strength. This gave no change of color, indicating the total absence of phosphates. As the nitric-molybdate reagent when employed with phenylhydrazin solution shows one part of P in 2,600,000, the test is an exceedingly sensitive one and consequently it may be relied on to indicate whether phosphates are wholly absent.

When, however, nitric acid of 30 per cent. strength was allowed to act on portions of either the nucleic acid or nucleoproteid for twenty four hours at 35°C., the addition of the nitric-molybdate reagent at once produced a precipitate which is immediately reduced to green or greenish-blue on the addition of the phenylhydrazin solution. That the yellowish precipitate is molybdo-

phosphate of ammonia was shown again and again by dissolving it in ammonia and precipitating it from the latter solution by adding concentrated nitric acid, when the characteristic crystals of the molybdo-phosphate,as shown under the microscope, were formed. The phosphate of this precipitate was also obtained as ammonio-magnesic phosphate. When the nitric acid was allowed to act for a longer time, *e. g.*, from two to six days, at 35°C., the quantity of phosphorus liberated as phosphoric acid was increased.

Quite a different result was obtained with caseinogen. The used quantity of the latter was purified by dissolving and precipitating five times and by extracting with ether to free it from lecithin. The material so prepared did not give the slightest evidence of the presence of phosphates when the nitric-molybdate reagent was added and immediately thereafter some phenylhydrazin solution (1 per cent.). When portions of the pure caseinogen were dissolved in nitric acid of 1.2 sp. gr., and kept at 35° C., for two weeks not the slightest trace of phosphoric acid was demonstrated with the nitric-molybdate reagent and phenylhydrazin, and even after two months only the slightest possible trace of phosphoric acid was present.

It is, therefore, to be concluded that phosphorus is combined in caseinogen in a manner very different from that which obtains in true nucleoproteids and that nitric acid may be employed to distinguish nucleic acids and the typical nucleoproteids from paranucleic compounds.

51 (194)

Does the stomach of the dog contain free hydrochloric acid during gastric digestion?

By **LAFAYETTE B. MENDEL.**

[*From the Sheffield Laboratory of Physiological Chemistry, Yale University.*]

In a recent contribution to the physiology of digestion from the Physiological Laboratory of the University of Vienna, Albert Müller[1] has made the announcement that the digestion of meat regularly proceeds in the stomach of healthy, normal dogs in the

[1] Albert Müller: *Archiv für die gesammte Physiologie*, 1907, cxvi, 163.

absence of *free* hydrochloric acid. He insists, further, that *free* HCl is lacking with all foodstuffs throughout the progress of gastric digestion in these animals. The total acidity is reported to reach high values in meat digestion and lower figures with other dietaries; but in each instance it is referable to *combined* acid. The ability of the dog's stomach to secrete a juice rich in *free* HCl is not questioned. In the case of this animal, however, Müller believes that the production of acid is limited by the demands of the digesting materials. As soon as the proteins present, or their cleavage products, are combined with acid, the further secretion of the latter ceases. The same behavior is said to characterize the gastric digestion of the cat; not, however, that of rabbits. Clinical experience further teaches that this description certainly does not apply to the digestive processes in the human stomach, where *free* HCl regularly occurs in a concentration of 1–2 per mille within a comparatively short period after a test meal.

These facts and ideas presented by Müller in respect to the chemical and secretory phenomena of gastric digestion in the dog were somewhat surprising to me in view of the experience gained in our laboratory,[1] on animals with gastric fistulas. In numerous experiments on two large dogs we uniformly found the acidity of the stomach contents to increase after a test meal of meat, until *free* HCl was present in not inconsiderable concentration. An illustrative protocol is reproduced here:

9.30 50 grams meat + 100 c.c. water fed.

Analysis of gastric contents; acidity expressed as HCl.

	Total acidity	Free HCl.
	%	%
10.00	0.299	0.090
10.30	0.475	0.122
11.00	0.518	0.173
11.15	0.497	0.241
11.35	0.494	0.202
11.50	0.479	0.195
12.10	0.382	0.187
12.30	Stomach empty; end of gastric digestion. Period of digestion, 3 hours.	

Müller calls attention to the difficulty of obtaining gastric contents from dogs through a stomach tube, owing to the fact that

[1] Chittenden, Mendel and Jackson: *American Journal of Physiology*, 1898, i, 193; also "Bicentennial Studies in Physiological Chemistry," Yale University, 1901, 105.

the digesting mass ordinarily forms a firm pulp unlike the semi-fluid contents of the human stomach. He therefore obtained the gastric contents by causing dogs to vomit after injections of apomorphine. Fifty trials made on 26 dogs after periods of 1, 2, 3, 4, and 6 hours with a single exception gave negative tests with Congo red paper, Günzburg's and Töpfer's reagents, although the digesting masses were always strongly acid to phenolphthalein.

In several of the more recent investigations[1] on the gastric digestion of dogs data are reported which indicate that fluid contents with little or no *free* HCl may be discharged through the pylorus. I have therefore undertaken additional experiments with the co-operation of Dr. Risley and Mr. Kleiner, to learn whether our original observations on fistula dogs are in any way unique. The dogs were given test meals of chopped meat (50–250 grams) with or without water, and samples of the gastric contents were removed at intervals through a stomach tube. By the simple device which we use for suspending the animals (and which was demonstrated) it is easy to obtain small portions for analysis. Frequently larger fluid portions (15–60 c.c.) were easily removed. They were filtered *at once* and tested qualitatively with Congo red paper, the tropaeolin 00 and dimethylaminoazobenzene reagents. Two c.c. were titrated *at once* with n/10 alkali, using Töpfer's reagent and then phenolphthalein as indicators for free HCl and total acidity.[2] Twelve test meals fed to five different animals furnished measurable quantities of *free* HCl in ten cases. Even more positive results might have been obtained if the removal of samples had been more advantageously timed. The dogs had in no case been fed since the preceding day. The accompanying summary of the essential data tells its own story.

The quantity of fluid gastric contents obtainable at any moment is never large in the dog. Nevertheless our experience scarcely justifies the assumption of a unique secretory regulation by which, as Müller assumes, acid is furnisheds ufficient only to combine with proteid material. For the cat also Cannon and Day[3] have

[1] Cf. e. g. Krehl: *Pathologische Physiologie*, 1904, 284; Lang: *Biochemische Zeitschrift*, 1906, ii, 240.

[2] Töpfer's method as modified by Einhorn: *New York Medical Journal*, 1896, xix, 603; cf. Chittenden, Mendel and Jackson: loc. cit., p. 191.

[3] Cannon and Day: *American Journal of Physiology*, 1903, ix, 402.

GASTRIC ANALYSIS.

Animal.	The test meal contained		Fluid contents removed.		Tests for free HCl were (+) positive or (—) negative with		Volume of $\frac{n}{10}$ alkali used for 2 c.c.	
Weight.	Meat.	Water.	Time.	Approximate quantity.	Tropaeolin oo.	Töpfer's reagent.	Total acidity.	Free HCl.
kgm.	gm.	gm.	hrs.	c.c.			c.c.	c.c.
A $13\frac{1}{2}$	150	100	2	52	—	—	2.2	0
			4	52	+	+	2.1	0.3
do.	150	300	1	12	—	—	0.8	0
			2	13	?	?	2.4	?
			$3\frac{3}{4}$	25	+	+	2.2	0.8
B 20	70	200	1	Small amount	—	—		0
do.	150	300	1	9	+	+	2.0	0.3
			2	1	+	+		
do.	150	300	1	30	—	—		
			2	47	+	+	2.7	0.7
do.	250	None	3	2	+	+	1.2	0.3
			$4\frac{1}{3}$	4	+	+	0.5	0.2
C 8	150	100	$2\frac{1}{2}$	3	+	+	1.5	0.4
			$3\frac{5}{6}$	13	?	+	2.3	0.4
do.	150	300	1	3	—	—	1.3	0
			2	5	+	+	1.9	0.3
			$4\frac{1}{2}$	3	+	+	1.6	0.5
D 12	100	200	1	68	—	—		
			2	29	+	+	2.6	1.2
do.	150	100	$2\frac{1}{3}$	38	?	+	3.2	0.4
			$3\frac{1}{2}$	8	+	+	2.0	0.6
do.	250	None	1	14	—	—	3.1	0
			3	3	?	+	1.8	0.3
			$4\frac{3}{4}$	1	—	?		
E 11	150	100	$1\frac{3}{4}$	36	—	—	1.6	0
			$3\frac{1}{3}$	—	—	—	2.0	0
			$4\frac{3}{4}$	16	+	+	2.0	0.8

stated that free acid may be present after a meal. As a possible explanation of these discrepancies, the differences between the methods of study used by Müller and by us may be of moment. It is not unlikely that when the semi-solid gastric contents are emptied *en masse* any free HCl present in the mixture speedily combines with the excess of unchanged proteid ejected, before digestion is stopped outside of the body. In all of our experiments, on the other hand, the material, analyzed at once, represented fluid contents as they were present in the stomach. The data furnished should therefore correspond with the composition of the soluble materials ready for propulsion along the digestive tract. At any rate some caution is necessary in the interpretation of the phenomena of gastric digestion recorded by the different investigators.

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On the nature of the process of fertilization.

By JACQUES LOEB.

[*From the Herzstein Research Laboratory of the University of California.*]

Two years ago I showed that the process of natural fertilization of the sea urchin egg could be imitated by the combination of two agencies: first the artificial production of a membrane around the egg and second the treatment of the egg for some time with hypertonic sea water. I expected that this imitation of the natural process of fertilization by external agencies might lead to a discovery of the ultimate chemical character of the process of fertilization and this proved to be true to that extent that I was able to show in a series of papers, published a year ago, that the essential effect of the natural or artificial fertilization is a calling forth of oxidations in the egg. These oxidations are the prerequisite for the synthesis of nuclein compounds from protoplasmic constituents of the egg, and this synthesis which forms the first stage in the developmental process. It may be that the formation of nucleins is an oxidative synthesis.[1]

When we produce artificially a membrane around the egg by treating the latter for a couple of minutes with a monobasic fatty acid, the egg forms after a certain time two astrospheres, but begins to disintegrate very rapidly. If the temperature is very low it may segment and even reach a blastula stage. I was able to show that the development as well as the disintegration only occur in the presence of free oxygen. If we substitute carefully washed hydrogen for the air in the sea water or if we prevent the oxidations in the egg by the addition of a trace of KCN to the sea water the eggs will neither develop nor disintegrate. From this I concluded that the process of membrane formation calls for or accelerates in the egg oxidations which lead to the formation of the two astrospheres and — if the temperature be sufficiently low — to a series of cell divisions. But these oxidations lead also to the

[1] Loeb: *Biochemische Zeitschrift*, i, p. 183, 1906; ii, p. 35, 1906. *University of California publications*, iii: p. 1, p. 33, p. 39, p. 49, 1906. *Pflüger's Archiv*, cxiii, 1906.

formation of toxic compounds which cause the comparatively rapid disintegration of such eggs. If, however, such eggs are put immediately or soon after they have gone through the process of membrane formation into hypertonic sea water for from 30 to 60 minutes, they may all develop at ordinary room temperature and a percentage of these eggs segments perfectly normally and develops into normal embryos. The hypertonic sea water has however this effect only when it contains free oxygen. If we substitute hydrogen for the air contained in it or if we prevent the oxidation in the egg by adding a trace of KCN to the hypertonic sea water, the eggs will not develop but disintegrate in the way characteristic for eggs with artificially produced membranes that have not been treated with hypertonic sea water. From this I concluded that the hypertonic sea water modifies the process of oxidation in the egg and leads the oxidations into the right channels. There remained, however, an apparent difficulty. In my original experiments on artificial parthenogenesis, not two but apparently only one agency was employed to cause the developement of larvæ from the unfertilized egg of the sea urchin, namely, an increase in the osmotic pressure of the sea water. My recent experiments here, however, show that in this purely osmotic method of artificial parthenogenesis, we are in reality dealing with a combination of two different agencies, one being the increase of the osmotic pressure at a comparatively low concentration of hydroxyl ions, the second the hydroxyl ions at a comparatively high concentration. The proof for this statement rests upon the following experimental facts.

(*a*) When the concentration of the HO is below a certain limit, namely, $10^{-6}n$ even the maximal increase of osmotic pressure fails to cause the formation of larvæ from the unfertilized eggs.

(*b*) When the concentration of hydroxyl ions is high, *e. g.*, $10^{-3}n$ a very slight increase of the osmotic pressure is able to call forth the formation of larvæ.

(*c*) The effects of the two agencies can be separated by first putting the eggs for from 1½ to 2 hours into a hypertonic solution with a concentration of hydroxyl ions between 10^{-7} and $10^{-6}n$ and afterwards transferring them for some time to an isotonic solution with a concentration of hydroxyl ions of about 2 or $4 \times 10^{-3}n$. While no egg that has been exposed to the hypertonic solution

will develop, many or possibly the majority of the eggs that have in addition been exposed to the hyperalkaline solution will develop into larvæ many of which are perfectly normal and rise to the surface. I have further found that the eggs which develop into larvæ very often (possibly always) have a membrane which, however, differs from the fatty acid membrane or the fertilization membrane in this, that it is not separated by so wide a space from the protoplasm and therefore easily escapes detection.

In a former paper I have already pointed out that the facts of natural fertilization agree also with the view set forth in the introductory remarks of this note.

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Comparative chemical composition of the hair of different races.

By **THOMAS A. RUTHERFORD** and **PHILIP B. HAWK.**

[*From the Laboratory of Physiological Chemistry of the Department of Medicine of the University of Pennsylvania.*]

Forty-five samples of hair were analyzed, the specimens being obtained from indian, negro, japanese and caucasian subjects. After subjecting the hair to the action of digestive juices and alcohol and ether the percentage content of sulphur, nitrogen, carbon and hydrogen in the remaining keratin was determined. The analyses indicate that the chemical composition of human hair is influenced by six factors, as follows: (1) Race of the subject; (2) sex of the subject; (3) age of the subject; (4) color of the hair; (5) purity of breeding of the subject; (6) whether the hair sample is obtained from a dead or living subject.

The *average* percentage composition of the forms of hair (keratin) analyzed is given below.

Subject.	Elementary percentage composition.					Ratio.
	S	N	C	H	O	S : N
Indian	4.82	15.40	44.06	6.53	29.19	1 : 3.2
Japanese	4.96	14.64	42.99	5.91	31.50	1 : 3.0
Negro	4.84	14.90	43.85	6.37	30.04	1 : 3.1
Caucasian :						
Adults	5.22	15.19	44.49	6.44	28.66	1 : 2.9
Children	4.93	14.58	43.23	6.46	30.80	1 : 3.0

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The oxidation of sugars by cupric acetate-acetic acid mixtures.

By **A. P. MATHEWS** and **HUGH MCGUIGAN.**

[*From the Laboratory of Biochemistry and Pharmacology, University of Chicago.*]

The study was undertaken to learn precisely upon what the oxidizing powers of cupric acetate and Fehling's solution depended. The addition of acetic acid to cupric acetate diminishes its speed of oxidation so that one sugar after another ceases to be oxidized at a rapid rate as more acid is added. The amount of acid that may be necessary to check the oxidation to any given rate depends on the concentration of the acetate; the more concentrated the acetate the more acid is required. McGuigan determined the amount of acid necessary to check oxidation of the various sugars in different concentrations of the acetate within a certain time (one half minute's boiling). The results showed that the sugars arranged themselves as follows according to the amount of acid necessary to check oxidation. Levulose (most acid required), galactose, glucose, maltose, lactose.

Solutions of different concentrations of acetate and acetic acid were prepared which would just fail to oxidize levulose to a visible reduction of cuprous oxide on one half minute's boiling. Similar solutions were prepared for the different sugars. Each of these solutions for any given sugar of one per cent. concentration had the same speed of oxidation.

The cupric ions in these solutions were measured by the electromotive force developed between the solution and a plate of copper. The hydrogen ions were determined by the inversion of cane sugar. From the figures thus obtained the result appeared that in all solutions oxidizing any one sugar with the same speed the decomposition tension of the cupric oxide in the solutions was a constant.

For the different sugars the following data for decomposition tension were obtained in those solutions that just failed to oxidize to a visible extent in one half minute's boiling.

Levulose,	0.583 volts.
Galactose,	0.562 "
Glucose,	0.558 "
Maltose,	0.532 "
Lactose,	0.519 "

The constancy of the decomposition tension shows that in solutions containing different concentrations of cupric acetate but having the same rate of oxidation of any single sugar, the product of the concentration of the cupric ions and the oxygen ions is a constant, or $C_{Cu^{++}} \times C_{\bar{O}} = K$. The fact that for the same rate of oxidation of the different sugars this product varies, shows that the per cent. of dissociation into reactive products of the different sugars also varies and in fact that levulose dissociates most, then galactose, glucose, maltose and lactose in a diminishing order. Preliminary observations indicate that for the same rate of oxidation, the product of $\dot{\dot{C}}u \times \bar{\bar{O}} \times$ *dissociated sugar molecules* is a *constant.*

The oxidizing *potential* of all solutions containing cupric ions appears to be constant; these solutions differ only in their *rates* of oxidation. Acid cupric sulphate is reduced by glucose, levulose, etc., but at a very slow rate. The constancy depends on the constant ionic potential of the cupric ions, regardless of their concentration. This potential is 0.668 volt. Fehling's solution differs from a cupric acetate-acetic acid solution not in its potential but only in its speed of oxidation. The superior speed of action of a Fehling's solution over a cupric acetate solution is due to the enormously greater concentration of oxygen ions (hydroxyl ions) in the Fehling's solution and also to the fact that the dissociation of the sugar molecule into active particles is enormously greater in an alkaline than an acid medium. (Schade: *Zeitschrift für physikal. Chem.*, 1906, lvii, pp. 1–46. Nef's work on glycols, etc.)

These facts show why it is that the sugars are oxidized and fermented by the tissues, by moulds and bacteria at different rates, this being due to the greater dissociation of certain sugars. A cupric acetate-acetic mixture of proper concentration will show the same selective action toward levulose that many bacteria and other living organisms show and oxidize the levulose almost completely before the glucose is attacked. Whether sugars differ also among themselves in their reducing *potential* has not yet been determined. No indications of such a difference have as yet occurred to us.

55 (198)

Observations on the effects of fasting upon the opsonic power of the blood to staphylococcus aureus.

By **ALLAN C. RANKIN** and **A. A. MARTIN** (by invitation).

[*From the Pathological Laboratory of McGill University, Montreal, Canada.*]

During the last year considerable work has been done in demonstrating the part that is played by opsonins in protecting the body from diseases, also in pointing out how the protective power of the body against certain bacteria can be accurately determined. The physiologists have frequently hinted that diminished nutrition lays the human body open for a ready invasion by micro-organisms, but they have not been able to support their views by actual figures. If we remember aright, at the last meeting of the British Medical Association at Toronto, Professor Chittenden referred to this matter and to the lack of absolute data, although we do not find that his remarks are included in the official report of the discussion in question.

One of us (M.), previous to entering as a medical student, had found that he could fast without serious result over a period of several days. Now, as a third year medical student, he decided that he was in favorable surroundings to undergo another fast during which observations upon metabolism might be taken. The results upon metabolism have been investigated by others. Here we desire to call attention to the effects of fasting for a period of nine days upon the opsonic power of the blood.

M. is a sturdily built young adult, twenty-eight years of age, who weighed before the fast one hundred and thirty-nine pounds and whose height is five feet and three-quarter inches. He had always enjoyed good health.

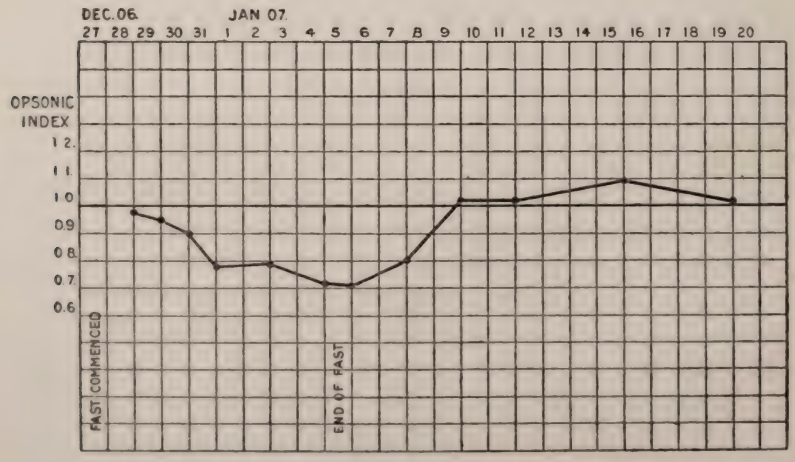
The fast began after a meal at 9 a. m. on December 27, and continued until 6 p. m., January 5. During this time M. did not suffer from boils or any infection which could have affected the results obtained in these observations. He was not at rest during this experimental fast but took daily exercise, frequently walking five miles and was up and about most of the day. He took water

to the amount of 200 cc. three times a day, but absolutely no food. At the conclusion of the fast his weight was one hundred and twenty-five pounds, a loss of fourteen pounds.

Unfortunately the fast had already begun when the other of us (R) was asked to make opsonic investigations. The first observation was then made on December 28th, thirty-six hours after the fast had started; the blood was taken at 8:30 p. m. From this date onwards observations were made daily, except on January 1st and January 3rd. The blood was drawn at the same hour each day (10 a. m.); on the last day, however, the blood was examined at 4 p. m., shortly before the conclusion of the fast.

After the fast the blood was examined five times over a period of two weeks. The blood was taken in the afternoon. An eighteen-hour culture of staphylococcus upon plain agar was used for the preparation of the emulsion. This organism was used on account of the fact that with it accurate results can be obtained and also on account of the fact that we were somewhat unprepared for the work which we took up hurriedly at a few hours notice. The control serum was that of an individual whose opsonic power had been shown (by pool) to be normal to this organism. The technique employed was that of Wright and Douglas.

The accompanying diagram gives a clear picture of the result obtained.



Examination of the curve shows that over the period of the fast there was a gradual diminution of the opsonic power till finally at the end of the fast, on the ninth day, it was 0.7.

We do not lay stress upon the small differences shown between some of the successive observations but we consider that the difference between 0.98 and 0.7 is absolutely definite.

We would call attention to the steady rise to and retention at the normal after the fast was broken.

We fully realize that a sweeping statement regarding the variations in the resistance of the body cannot be made from our observations on the opsonic power against staphylococcus aureus; nevertheless, it is of interest that a decided fall in the power did occur against this organism. Moreover, if we take it that the natural opsonins which exist in the body are general and not specific, it would not seem unlikely that the phagocytic index against other organisms could be shown to be diminished correspondingly.

56 (199)

The automatism of the respiratory center.

By **G. N. STEWART** and **F. H. PIKE.**

[*From the Hull Physiological Laboratory, University of Chicago.*]

In the course of observations on the resuscitation of the central nervous system we have had the opportunity to determine whether regular, spontaneous respiratory movements can be discharged at a stage in the resuscitation when as yet the respiratory center is unaffected by stimulation of afferent nerves. The respiratory movements, and usually the arterial blood pressure as well, were recorded and the effect of stimulation of the central ends of the vagus, brachial plexus and sometimes the sciatic determined before occlusion of the arteries supplying the brain, the bulb and the upper portion of the cervical spinal cord. These arteries (innominate and left subclavian proximal to the origin of the left vertebral) were then occluded by temporary ligatures. At intervals during the occlusion and again after releasing the vessels the nerves were stimulated, of course with the same strength of stimulus as before. Artificial respiration was kept up from the time when natural res-

piration ceased till it was thoroughly re-established after resuscitation.

Result. — An interval, varying in length with the duration of the occlusion and other circumstances, was found during resuscitation, when spontaneous respiration had returned and was going on with a regular rhythm while totally incapable of being influenced by stimulation of any of the afferent paths investigated. The most probable assumption is that at this stage some portion of these afferent paths to the respiratory center was still unable to conduct impulses to the center, the block being possibly (in terms of the neurone hypothesis) in the synapses in which the afferent fibers terminate in the bulb. Resuscitation of the center and the efferent paths from it had at this stage been carried to the point at which the motor impulses were able to pass down to the anterior horn cells which innervate the muscles of ordinary respiration. If at this point in the resuscitation the afferent paths of the vagus and the brachial plexus are still interrupted, it is reasonable to assume that the same is true of the other afferent fibers connected with the bulbar respiratory center. For certainly of the fibers running headwards to the bulb none can be supposed to be more favorably situated for carrying impressions to the respiratory center than the afferent fibers of the vagus. Nor can it be imagined that at this time impulses can be passing to the center from the higher parts of the brain, since it is a general rule that the nervous structures higher than the bulb require a longer time for resuscitation than the bulb or the spinal cord does.

Conclusion. — The method described seems indeed to afford, what has long been a *desideratum*, a means of temporarily eliminating all the afferent paths connected with the respiratory center. Since under these conditions the center continues to discharge itself in such a way as to maintain a long and unbroken series of regular, efficient respiratory movements, its normal activity is to be considered an example of physiological automatism, not originated, although influenced by afferent nervous impulses.

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A series of spontaneous tumors in mice.

By **E. E. TYZZER.**

[*From the Laboratory of the Caroline Brewer Croft Cancer Commission, Harvard Medical School.*]

In the investigation of tumors in mice, attention has been, for the most part, directed to those which develop in the subcutaneous tissue. It is possible that internal tumors often occur unnoticed. In this series the tumors of the lung are most frequent.

Primary, papillary, cyst-adenomata of the lung have been found in eleven cases. All these tumors conform to one type, and consist of cuboidal or columnar epithelium covering irregular folds and processes of connective tissue. No mitotic figures have been found in the epithelium of these tumors, so that it is evident that they are not rapidly growing. Most of these tumors were very minute and in several instances, when they occurred with other primary tumors, they were mistaken for metastases until examined histologically. In one case a tumor of this type attained such size that it filled about one third of the thorax. In two other cases tumors were found growing into the bronchi. These tumors occur in both male and female, and appear to be about equally frequent in the inoculated and non-inoculated mice. The largest of the lung tumors was inoculated into five mice, but failed to develop further.

Minute adenomata of the kidney were found in two cases.

A rapidly growing lympho-sarcoma, which occurred in an old female mouse, was inoculated into seventeen mice with negative results.

Tumors of the mammary gland have developed in three old female mice, and in each case the lymphatics were invaded by the growth. In the first case the primary tumor presents, in addition to simple adenoma, transitions from this to an actively growing carcinoma. Another adeno-carcinoma of the mammary gland occurred in a waltzing mouse. The tumor is peculiar in that groups of the epithelial cells become vacuolated, and resemble very closely the sebaceous glands of the skin. The inoculation

of this tumor into other waltzing mice has been successful in one instance. The growth in this case is relatively slow. A third subcutaneous adeno-carcinoma, differing in structure from both of the preceding ones, has been inoculated into a number of mice, which are now under observation.

Thus in the experimental inoculation of four spontaneous tumors into other mice, a new growth has followed with one only.

An important fact in this series is the relative frequency with which single cases present more than one primary tumor. In three mice there were in each two primary spontaneous tumors of different types. In several other cases a primary tumor occurred in a mouse in which there was also an inoculated tumor.

The mice under observation are kept in small cages, which are kept as clean as possible and scrubbed periodically with hot water and soap. In the seventeen tumors, of this series, there has been no definite indication of cage-infection. On the other hand the frequency of tumors in certain families of mice has suggested the possibility that heredity plays a part in the occurrence of tumors. Certain families of mice, which are susceptible to the inoculable tumors, have developed spontaneous tumors; other families, which are not susceptible to the inoculable tumors, have never developed spontaneous tumors. Since heredity is unquestionably a factor as regards the growth of the inoculable tumors, it should also be considered as a possible factor in the development of spontaneous tumors. Breeding experiments have thus far furnished results in accord with this hypothesis.

Since it has been demonstrated that spirochetæ occur frequently in tumors of mice, silver preparations have been made of several of the tumors of this series, following the technic of Levaditti. No spirochetæ were found in the lympho-sarcoma, but they were found in small numbers in the tumor of the Japanese waltzing mouse. The skin covering this tumor had not ulcerated.

Spirochetæ were also found in the stroma of an inoculated tumor of the Jensen strain. None were found in several human cancers and in an actively growing sarcoma of a hen.

Silver preparations were made of the tissues of several mice which had no tumors. One mouse which had been twice inoculated with the Jensen tumor, died six weeks after the last of the

inoculations. Enormous numbers of spirochetæ, apparently identical with those which occur in the tumors of the mouse, were found in the myocardium and in the lung.

Another mouse, twice inoculated with the Ehrlich "Stamme II" tumor, died three months after the second inoculation. Neither of the inoculations was followed by any growth of the tumor. There was a long-standing inflammation of one foot and leg. Spirochetæ were found in small numbers about the inflammation in the foot, and in enormous numbers in the mediastinum about the bronchi and large veins. The tubules of the kidney also contain large numbers, but they here appear to be undergoing disintegration and and are not so readily distinguished. The organisms in these two cases are of the form of a relatively thick, broad spiral, and have at one end a flagellum, which is less intensely colored than the body of the organism.

The spirochetæ found in these two cases appear to be identical with those found in the tumors of the mouse.

58 (201)

Concerning the neutrality of protoplasm.

By **LAWRENCE J. HENDERSON** (by invitation).

[*From the Laboratory of Biological Chemistry of the Harvard Medical School.*]

It is desirable, both on account of the normal production of acid during metabolism, and because of the production of acid under pathological circumstances, to study the adjustment of equilibrium in protoplasm whereby neutrality is maintained. In undertaking this study the equilibrium in mixtures of sodium hydrate, phosphoric acid and carbonic acid has been studied.

As a result of the investigations it appears that in the presence of both free and combined carbonic acid in measurable amount, such mixtures are precisely neutral to rosolic acid, and that the amount of sodium bicarbonate in such mixtures can vary greatly without great variation in the ratio between mono-sodium phosphate and di-sodium phosphate. These results are in accord with the theory, based upon the ionization constant of carbonic acid

(3×10^{-7}) and of the ion H_2PO_4 (2×10^{-7}). Although the equilibrium in such a system at 40° C. may be somewhat different it is evident that this equilibrium is calculated almost perfectly to protect protoplasm from variation in neutrality. The variation in hydrogen and hydroxyl ionization can hardly be more than 5×10^{-7}.

The theory of the transport of carbonic acid is now being investigated in the light of this great variation of combined carbonic acid, and the variation which has been found in "acidosis."

59 (202)

The influence of adrenalin upon the venous blood flow.

By **RUSSELL BURTON-OPITZ.**

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

The blood flow in the femoral, external jugular and azygos veins was measured by means of the stromuhr described by the author. During the experiment, solutions of adrenalin were injected centrally to the stromuhr. The effect of the adrenalin showed itself in a retardation of the venous inflow which appeared in from 14–16 seconds after the injection. Considering the velocity of the venous blood stream, it must be assumed that the adrenalin did not produce its characteristic effect until it had reached the arterial side of the circulatory system. The experiments tend to disprove the existence of vaso-motor nerves in the central veins and the pulmonary circuit.

60 (203)

The viscosity of laked blood.

By **RUSSELL BURTON-OPITZ.**

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

It was found that the viscosity of laked blood prepared by the process of freezing, is very much less than the viscosity of defibrinated blood. The specific gravity was only slightly lessened.

Examples of the experimental data are appended:

Defibrinated Blood		Laked Blood	
Spec. Grav.	Viscosity	Spec. Grav.	Viscosity
1.0566	665.74	1.0563	982.35

61 (204)

The determination of ammonia and urea in blood.

By **W. McKIM MARRIOTT** and **C. G. L. WOLF.**

[*From Cornell University Medical College, New York City.*]

Ammonia is determined by distillation in vacuo. 100 c.c. of blood are treated with 50 c.c. of saturated sodium chlorid solution and 250 c.c. of methyl alcohol are added to the mixture. The precipitate formed is finely granular. The residue is filtered off in a filter press, and the filtrate distilled for 40 minutes, with the temperature of the water bath at 40–50°C. The receivers are charged with $n/50$ sulphuric acid, and the acid titrated with $n/50$ sodium hydroxid free from carbonate. Sodium alizarin sulfonate is used as an indicator. The results are perfectly accurate.

The residue after distillation is made acid with hydrochloric acid, evaporated and hydrolyzed with 10 grams of glacial phosphoric acid at 150°C. The ammonia formed from the urea is then distilled into $n/50$ acid. The duplicates have shown very satisfactory agreement, but it is quite certain that not all the urea which is added to a sample of blood is recovered. It is probable that the carbohydrates in the residue combine with the urea at the temperature of hydrolysis and prevent the formation of ammonia.

62 (205)

The resolution of fibrinous exudates, with exhibition of specimens.

By **EUGENE L. OPIE.**

[*From the Rockefeller Institute for Medical Research.*]

The purpose of the experiments which are described has been to determine the part played by enzymes in the resolution of a fibrinous exudate. When turpentine is injected into the subcutaneous tissue of the dog, an abscess results, but when an equal

quantity of turpentine is injected into the pleural cavity, there is abundant exudation of coagulable fluid and the serous surfaces are covered by thick layers of fibrin. Accumulation of fluid which can be followed during life by percussion of the animal's chest reaches a maximum at the end of three days, and then gradually subsides so that at the end of six days, in most instances, the cavity contains no fluid. Fibrin, though diminished in amount, is still present, and gradually disappears, so that at the end of two or three weeks, the cavity has returned to the normal, save for a few organized adhesions.

During the early stage of the inflammation, fibrinous exudate, freed from the serum by washing in salt solution, undergoes digestion when suspended in an alkaline (0.2 per cent. sodium carbonate) or in an acid medium (0.2 per cent. acetic acid). At the end of six days, at a time when fluid has disappeared from the pleural cavity, digestion fails to occur in an alkaline medium, but occurs with great activity in the presence of acid.

During the first stage of the inflammatory reaction, when fluid is abundant and the fibrin which is present digests in the presence of alkali, polynuclear leucocytes are very numerous in the meshes of the fibrin. In the second stage, when fluid has in great part disappeared, and the fibrin contains only one enzyme digesting in the presence of acid, polynuclear leucocytes have disappeared and only mononuclear cells are embedded in the fibrin.

Since the acids, which, in vitro, favor the action of the enzyme present in the second stage of the process, do not occur in the body, the possibility has suggested itself that carbon dioxide brings this enzyme into action. If carbon dioxide is passed through normal salt solution in which strips of such fibrin are suspended, digestion is very greatly hastened. The normal inhibition exerted by blood serum upon the enzyme is overcome by carbon dioxide; in the presence of a small quantity of blood serum, carbon dioxide causes greater enzymotic activity than in the presence of salt solution alone.

63 (206)

Extirpation of both kidneys from a cat and transplantation of both kidneys from another cat, with exhibition of specimens.

By **ALEXIS CARREL.**

[*From the Rockefeller Institute for Medical Research.*]

Both kidneys from a cat were extirpated and immediately replaced by both kidneys from another cat.

After this operation the animal urinated abundantly. Urine collected during the first few days contained albumin. On the fourteenth day, the cat was operated on for hernia of the small intestine through the abdominal wound. The animal died from general peritonitis one day after this second operation.

The anatomical specimen shows that the kidneys are a little enlarged. There is a slight hydronephrosis on the left side. Nevertheless, both organs appear to be in good condition.

Twenty second meeting.

Rockefeller Institute for Medical Research. April 17, 1907. President Flexner in the chair.

64 (207)

Wounds of the pregnant uterus.

By **LEO LOEB.**

[*From the Laboratory of Experimental Pathology, University of Pennsylvania.*]

In continuation of former experiments to determine the influence of functional conditions upon processes of cell growth and cell necrosis in the ovaries, investigations of a similar character were undertaken on the pregnant uterus of the guinea pig. As is well known, the pregnant uterus responds to the stimulation of the fertilized ovum by the production of decidual tissue. It was thought possible that in the beginning of pregnancy the uterus might respond also to other stimuli such as wounds, in a way different from the ordinary uterus. Experiments were carried out in twenty six guinea pigs at different stages of pregnancy. Wounds were made in various directions in the uterus, or part of the wall of the uterus was inverted so that the mucous membrane was turned outside. It was found that at a certain stage of pregnancy, namely from the fourth to the sixth day, nodules of decidual tissue were formed at places where the continuity of the uterus had been interrupted or where the mucous membrane had been inverted. Serial sections of these nodules show that they consist of typical decidual tissue which does not include a developing ovum. The number of these nodules was either larger than the number of corpora lutea present in the ovaries which had been cut into serial sections or in other cases corpora lutea were present on only one side of the animal while the decidual nodules were present in both horns of the uterus. Under those conditions it is not likely that the formation of the decidual nodules was caused by the direct stimulation of an ovum, but it is more likely that, at the period of pregnancy, when the development of

decidual tissue begins to take place normally, other stimuli are also able to call forth the production of decidual nodules. At the present stage of the investigation I do not, however, wish to deny positively that a brief contact of the ovum with a wound of the uterus or with the inverted mucous membrane of the uterus is necessary for the production of decidual nodules. Between the third and fourth week after impregnation such nodules become necrotic. They resemble small tumors which originate under chemical stimulation, and are of a transitory character because the stimulus is transitory. They might be called benign deciduomata and be classed among that variety of new growths which I designated as transitory tumors and of which the corpus luteum might serve as a prototype. Among the animals experimented upon in the first three days of pregnancy, only once a deciduoma was found.

These experiments may also be of interest in so far as they seem to show that under ordinary conditions it is not possible to produce an abdominal pregnancy in the guinea pig by various injuries of the uterus; although it may be assumed that under the conditions of the methods of experimentation adopted by me, the ovum had, in many cases, easy access to the abdominal cavity. In no instance did the peritoneal cavity show any change in the course of these experiments. We may, therefore, assume that the entrance of the ovum into the abdominal cavity is usually not sufficient to produce an abdominal pregnancy.

65 (208)

The effect of light on the staining of cells.

By **LEO LOEB.**

[*From the Laboratory of Experimental Pathology, University of Pennsylvania.*]

Former studies of the structural changes in blood cells, especially of the behavior of cell granules under the influence of different external conditions, made it desirable to investigate the behavior of cells in different staining solutions, especially in solutions of vital stains. In the course of various investigations, it was found that solutions not only of eosin but also of other stains, as neutral red, affect the cells very differently in light and in dark. That eosin and other fluorescent substances are much more poison-

ous for cells and for ferments in light than in dark has been previously shown by von Tappeiner, Raab and a number of others. The results of my investigations which were carried out (partly with the coöperation of Mr. L. P. Shippen) in the summers of 1905 and 1906, the last experiment having been done at the end of August, 1906, may be summarized in the following way:

1. In solutions of dyes (neutral red, eosin, methylene blue, methyl violet and others), cells (eggs of Asterias) are stained differently according to whether the cells and solutions are exposed to the light or kept in the dark.

2. Combination of an acid and a basic dye (eosin and methylene blue) increased markedly the differences in the staining of the cells in the light and in the dark, in so far, as a small addition of methylene blue to eosin suffices to increase very much the staining reaction which is characteristic for light. The same holds good, probably, for other combinations, as neutral red and eosin. A mutually neutralizing or antitoxic effect of basic and acid dyes does, therefore, not exist. This increase in the effect of a combination of methylene blue and eosin is not caused by a primary change which the light produces in the solutions. Solutions of dyes which have been previously exposed to light do not stain the cells in the dark differently from solutions which had not been exposed to the light. In a combination of two basic dyes (methylene blue and neutral red) methylene blue and neutral red substitute each other in the dark according to the proportions in which they are mixed. In the light the cells assume a tone intermediate between neutral red and methylene blue.

3. The difference in the staining of cells in the light and dark is caused by at least two different effects of the light. (*a*) The light causes primary changes in the cells, and the difference in the staining of cells in the light and in the dark is caused by those primary changes which the light produces in the cells. This applies to staining with eosin, neutral red and with certain mixtures of eosin and methylene blue and eosin and neutral red. (*b*) The light changes primarily the staining solutions and the staining of the cells corresponds to the primary changes in the staining solutions. This applies to staining with pure methylene blue and to such mixtures of methylene blue and eosin in which much methy-

lene blue is present. It also applies, perhaps, to solutions of hematoxylin. The staining of the cells in the light as well as in the dark depends also upon the proportions in which both dyes are present in the mixture.

4. It is possible to distinguish the two factors stated under *a* and *b* by killing the cells with heat. The effect of light upon the cells which is caused by its direct action upon the cells, disappears if the cells have been previously killed. The changes, on the contrary, which are secondary to the primary changes in the staining solutions are still present.

5. Means which diminish the oxidative processes in the cells (*e. g.*, addition of KCN, by which hydrogen is carried through the solution) and saturation of the solution with oxygen, do not modify markedly the differences in the staining of the cells in the light and in the dark. It is, therefore, not probable that the light influences the staining of the cells by causing an increase in the oxidative processes. The addition of alkali to the staining solution is likewise without influence upon the staining of the cells in the dark and in the light.

6. A series of observations on the behavior of different ova and larvæ in the different staining solutions render it probable that the influence of the light depends partly at least upon the injury or death of cells which is caused by light, if the cells are in staining solutions, and that the differences in the action of the stains are therefore secondary. Actively swimming blastulæ and gastrulæ stain differently with eosin on the one hand, and with neutral red and methylene blue on the other hand. With the two latter dyes, especially with neutral red, the external layers of healthy cells are stained. With eosin, on the other hand, those cells of blastulæ and gastrulæ are stained which were cast off either into the inner cavity or to the outside of the organisms.

66 (209)

The abolition of visceral pain by intramuscular injection of cocaine. — A demonstration.

By **L. KAST** and **S. J. MELTZER.**

[*From the Rockefeller Institute for Medical Research.*]

The chief purpose of the demonstration was to bring out a new point with regard to the effects of cocaine. But we wish to utilize the experiment also in settlement of an old and frequently discussed point, namely, the question of the sensation of pain in abdominal viscera. According to the latest review of that subject in Nagel's Handbook of Physiology, the majority of the writers are inclined to deny the existence of such sensations.

On this dog laparotomy was performed under ether anesthesia and one intestinal coil was loosely fixed between the branches of a long clamp; the abdomen was again closed by sutures with the exception of a small opening for the body of the clamp. Compression of the protruding handles of the clamp meant pressure upon the coil. At the time of demonstration the animal was not entirely out of the anesthesia; nevertheless even a moderate compression of the handles sufficed to bring out an unmistakable reaction. Simple traction had apparently no effect and rubbing the clamp within the wound or rubbing the inner point of the clamp against the parietal peritoneum had only a slight effect.

This experiment demonstrates then beyond a doubt that the *intestines of dogs are not devoid of the sensation of pain.*

An injection of 0.02 gm. of cocaine was then made into the pectoral muscle. Five minutes later the handles of the clamp could be compressed or moved in any other manner without bringing out any reaction, while the animal had his eyes wide open. This shows clearly that *cocaine can produce not only local anesthesia but also a distant anesthetic effect through the circulation.*

67 (210)

The effect of nephrectomy upon the toxicity of magnesium sulphate when given by mouth. — A demonstration.

By **S. J. MELTZER.**

[*From the Rockefeller Institute for Medical Research.*]

Three rabbits were shown, one normal and two nephrectomized. The nephrectomy was performed nine hours before the demonstration. One nephrectomized animal received by mouth, soon after the nephrectomy, magnesium sulphate (6 grams per kilo in a 25 per cent. solution). The normal animal received by mouth 7 grams per kilo of the same salt. The other nephrectomized rabbit received no magnesium sulphate. At the time of the demonstration the nephrectomized rabbit which had received the salts was under profound anesthesia with complete muscular relaxation, while the other two animals were in an apparently normal state. This shows that in *nephrectomized rabbits magnesium salts produce a profound general effect even when given by mouth, and that the absence of such an effect in the usual administration of the salts is due to the comparatively prompt elimination through the kidneys of a large part of the absorbed salts, thus preventing at any given time the accumulation within the organism of a quantity equal to a toxic dose.*

68 (211)

Observations on a rabbit for thirty months after the removal of the superior cervical ganglion.

By **S. J. MELTZER.**

[*From the Rockefeller Institute for Medical Research.*]

Langendorff[1] reported that in one experiment on a cat one hundred and five days after the removal of the superior cervical ganglion, the paralytic symptoms of the eye disappeared, and stimulation of the cervical sympathetic nerve caused the typical effects. Microscopically no nerve cells could be detected, and Langendorff assumed that there was a union between the preganglionic and postganglionic nerve fibers. Langley,[2] on the other

[1] Langendorff: *Centralblatt für Physiologie*, xv, 483, 1901. The number of days is quoted here from Langley and Anderson; it is not mentioned in the *Centralblatt.*

[2] Langley: *Journal of Physiology*, xxv, 417, 1900.

hand, reported, about one year before Langendorff, an experiment on a cat in which twenty-three months after the removal of the superior cervical ganglion stimulation of the cervical sympathetic did not produce the usual effects, and on microscopical examination some postganglionic nerve fibers were found to have been regenerated; but there were neither nerve cells nor any union between the postganglionic and preganglionic nerve fibers. Later Langley and Anderson[1] repeated the experiment on eight cats. In six of the animals, which lived between one hundred and eighty-three and four hundred and seventy-six days, the paralytic symptoms remained permanent, and stimulation of the cervical sympathetic caused no effect. In two of the cases there was some decrease in the paralytic symptoms, and stimulation of the cervical sympathetic caused some effect, but microscopical examination showed that in both cases not all of the nerve cells had been removed.

All the above experiments were made on cats, which have a large ganglion. The gap between the postganglionic and preganglionic nerve fibers in the cat is nearly one centimeter. In the rabbit the ganglion is barely three millimeters long, and there might perhaps be a better chance for a final union of the nerve fibers of the two poles of the ganglion. I am going to report here briefly some observations made on a rabbit which lived over thirty months after the removal of the superior cervical ganglion.

Full grown, grey, male rabbit. Left superior cervical ganglion removed October 14, 1904. Animal died April 23, 1907.

Soon after the removal of the ganglion the left pupil became quite small; a few days later it became somewhat wider again, and some weeks later it became constricted to about the original size after the operation and retained this size permanently until death. The blood vessels of the left ear, which became wider after the removal of the ganglion, gradually assumed the size of the vessels of the other ear and remained in that state permanently. *During the last eighteen months the blood vessels of both ears were never very wide and showed but little of the usual rhythmical changes.*

We[2] have shown that after removal of the ganglion, a sub-

[1] Langley and Anderson: *Journal of Physiology*, xxxi, 383, 1904.

[2] S. J. Meltzer and Clara Meltzer Auer: *American Journal of Physiology*, xi, 28, 1904.

cutaneous injection or an instillation of adrenalin into the conunctival sacs of the rabbit causes a dilatation of the pupil on the side from which the ganglion was removed. This *biological test for the absence of the ganglion* was frequently made within the two and a half years of the animal's life and it was found that a *subcutaneous or intramuscular injection or an instillation of adrenalin invariably caused a long lasting dilatation of the left pupil.* This test seemed to prove satisfactorily that the ganglion was not regenerated, or at least the postganglionic and preganglionic nerve fibres did not grow together. To obtain further proof, twenty-eight months after the removal of the ganglion the cervical sympathetic nerves of both sides were exposed and stimulated with induction currents. While stimulation of the right sympathetic easily caused the usual effects upon the ear vessels and pupil of the corresponding side, *stimulation of the left cervical sympathetic caused no changes whatsoever in the left pupil or in the vessels of the left ear.*[1]

During the last twelve months there were, however, a few changes which deserve to be mentioned. In the first place the dilatation of the left pupil never attained the same degree as during the first period. Further an intramuscular injection of adrenalin, which in the early period brought out the dilatation of the pupil within two or three minutes,[2] now developed its effect very slowly. Finally the constricting effect of eserin was only partly overcome by an injection or instillation of adrenalin, whereas in the early period the effect of eserin was completely overcome by adrenalin. Apparently the relations of adrenalin to the dilator pupillæ had somehow undergone some changes. Local stimulation of the iris was not tested.

I shall record the following observations without offering for the present any interpretation of them. Within the last ten months the *right pupil was permanently distinctly larger than normal and responded sluggishly to light. An injection of adrenalin brought out a distinct constriction* which lasted about fifteen minutes. After the above mentioned stimulation of the cervical sympathetics, *the permanent dilation of the right pupil disappeared for about five*

[1] This experiment was carried out in the presence of Drs. Flexner, Opie and Carrel.

[2] S. J. Meltzer and John Auer: *Journal of Experimental Medicine*, vii, 59, 1905.

weeks and an injection of adrenalin had no effect upon the pupil. For the last three weeks the dilation of the right pupil had again returned.

On account of the very moderate effect which the intramuscular injection of adrenalin had caused in the left pupil in the last few days, an intravenous injection of adrenalin was tried on this animal for the first time. Not more than 0.3 c.c. of adrenalin (1 : 1000) were given through the ear vein. The right pupil remained unchanged, fairly dilated. *The left pupil became gradually dilated* so that after an hour the dilation was at the maximum. Half an hour later the animal fell over on its side, blood and foam escaping through the mouth and nose. The rabbit died of acute pulmonary edema.

At the autopsy, no sign of a ganglion could be discovered macroscopically on the left side; in the neighborhood of the seat of the ganglion the sympathetic nerve was lost in strands of connective tissue. (The abdominal aorta showed a few sclerotic patches.)

69 (212)

Intra-abdominal pressures.

By **HAVEN EMERSON.**

[*From the Department of Physiology of Columbia University, at the College of Physicians and Surgeons.*]

Definition:

1. Pressures upon solid viscera.
2. Pressures within hollow viscera.
3. Pressures within blood and lymph vessels.
4. Pressures within the free peritoneal cavity.

Pressures upon solid viscera cannot be other than those present in the free peritoneal cavity.

Pressures within hollow viscera have been fairly established.

Pressures within blood and lymph spaces have been accurately determined.

Pressure within the free peritoneal cavity has been a subject of disagreement since 1865 when Braune declared it was negative.

To determine the normal pressure and its variations within the peritoneal cavity a perforated trocar was used to pierce the abdom-

inal wall. This was connected with a water manometer arranged to record by a float and marker upon a smoked paper.

In dogs the pressure varied from 2–45 mm. of water above atmospheric, *i. e.*, positive.

In cats from 2–20 mm. positive.

In rabbits from 2–25 mm. positive.

In calves from 2–10 mm. positive.

The causes of this persistent but fluctuating positive pressure within the free peritoneal cavity are the tone of the muscular walls of the peritoneal cavity, including the diaphragm and the pelvic floor.

The contraction of the diaphragm is the chief, if not the only factor in the normal rise in pressure during inspiration.

Debilitated states show a low pressure.

Ether anesthesia causes a gradual drop in pressure until with complete loss of muscular tone, the pressure reaches zero.

Curare likewise causes a progressive fall to zero pressure.

Asphyxia develops great rises in pressure during inspiration until muscular relaxation allows a drop to zero just before death.

Excessive pressure artificially produced within the peritoneal cavity causes death from cardiac failure before the obstruction to respiratory excursion has developed a marked asphyxia.

The pressure is the same at all points of the peritoneal cavity, and is subject to identical variations wherever the recording trocar is placed.

The physiological function of these pressure conditions seems to be chiefly in assisting the circulation of blood and lymph, thereby playing an important role in the processes of absorption and elimination which take place within the abdomen.

Clinical observations in diseased conditions are under way.

70 (213)

On the influence of CO_2 on the viscosity of the blood.

By RUSSELL BURTON-OPITZ.

[*From the Physiological Laboratory of Columbia University, at the College of Physicians and Surgeons.*]

It has been proved by the author[1] that the blood in the veins possesses a somewhat greater viscosity than the blood in the arteries. As this difference is caused no doubt by the greater amount of CO_2 present in the venous blood, it became of some consequence to determine whether the arterial blood could be made to assume a greater viscosity by increasing its CO_2 content.

The dogs used in these experiments received alternately a supply of normal air and air charged with CO_2. During the period of inhalation of the air plus CO_2 the arterial blood showed a somewhat greater viscosity than during the time when the animal breathed normal air. The changes appeared very promptly, but were never very conspicuous. The specific gravity of the blood pursued a course parallel to that of the viscosity.

71 (214)

Agglutinins and precipitins in anti-gonococcic serum.

By JOHN C. TORREY.

[*From the Department of Experimental Pathology, Loomis Laboratory, Cornell University Medical College.*]

In December, 1906, I described the action and method of production of an anti-gonococcic serum which gave evidence of being of therapeutic value in the treatment of gonorrheal arthritis. At the time announcement was made of the fact that the serum contained specific agglutinins and precipitins for gonococcus. Since then a detailed investigation into the nature of these anti-bodies has been carried on. The results of this study may be summarized as follows:

1. Rabbits and other laboratory animals, when inoculated with cultures of gonococcus, raise specific agglutinins and precipitins.

[1] This journal: 1903, i, p. 23.

2. Normal rabbit sera contain a varying amount of agglutinin for gonococcus.

3. Strains of gonoccoci differ greatly in the titer of their agglutination with various gonococcic immune sera.

4. After one inoculation with a certain culture a large amount of agglutinin was produced for some strains, but none for others. Further inoculations caused an increase in the titer of the agglutination for certain strains but a drop in that of others.

5. Absorption experiments indicate that an anti-gonococcic serum may contain, in addition to the specific homologous agglutinins, several groups of agglutinins which act on the different cultures quite independently of one another. At least three groups were found, whose major or specific agglutinins are not removed by inter-absorptions. This indicates that as far as agglutination is concerned there are specific differences between these groups. The family gonococcus is, accordingly, heterogeneous rather than homogenous, and in that respect resembles the dysentery, colon and streptococcus families. In making a serum for therapeutic purposes, this fact should be borne in mind.

6. The passage of a culture of gonococcus through a guinea-pig caused a very marked decrease in its agglutinability.

7. With the exception of one serum, meningococcus agglutinated only in low dilutions of the anti-gonococcic sera.

8. Anti-gonococcic serum contains specific precipitins for gonococcus.

9. There appeared to be no relation between the precipitating and the agglutinating properties of an anti-gonococcic serum for a culture of gonococcus.

10. Anti-gonococcic sera contain as a rule some precipitins for meningococcus, but none for m. catarrhalis or staphylococcus.

11. There is evidence, according to my experiments, of a relationship between gonococcus and meningococcus, but not of as close a one as has been described by some investigators.

72 (215)

On the separate determination of acetone and diacetic acid in diabetic urines.

By **OTTO FOLIN.**

[*From the Chemical Laboratory of McLean Hospital, Waverley, Mass.*]

The Messinger-Huppert method is valuable for the determination of acetone and diacetic acid in urine but it gives only the sum of these two products and there is manifestly need of an additional quantitative method for the separate determination either of acetone or of diacetic acid.

While acetone is a liquid with a boiling point of 56°C. and dissolves in water in all proportions, I have found that it can be removed from its solutions by means of an air current and at ordinary room temperatures even more readily than ammonia. It can be determined in about half an hour, according to the same principle and by the help of the same apparatus which I use for the determination of ammonia. The determination is made as follows :

Measure 20–25 c.c. of acetone solution or urine into an aerometer cylinder and add 0.2–0.3 gm. oxalic acid or a few drops of 10 per cent. phosphoric acid, 8–10 gm. sodium chloride and a little petroleum. Connect with the absorbing bottle (as in the ammonia determination) in which has been placed water and 40 per cent. KOH solution (about 10 c.c. of the latter to 150 c.c. of the former) and an excess of a standardized solution of iodine. Connect the whole with a Chapman pump and run the air current through for 20–25 minutes. (The air current should be fairly strong but not as strong as for the ammonia determination.) Every trace of the acetone will now have been converted into iodoform in the receiving bottle. Acidify the contents of the latter by the addition of concentrated hydrochloric acid (10 c.c. for each 10 c.c. of the strong alkali used) and titrate the excess of the iodine, as in the Messinger-Huppert method, with standardized thiosulphate solution and starch.

The determination of the acetone can be made simultaneously with the determination of the ammonia with the use of the same air current and even in the same sample of urine but I do not

recommend such a combination except for cases where the amount of available urine is small.

In order to obtain reliable results by this method it is necessary to observe certain precautions.

No time should be wasted after the alkali has been added to the standardized iodine solution because the potassium hypoiodite in the latter changes gradually to potassium iodate which is not available for the formation of iodoform. The alkaline iodine solution must not touch rubber. The absorption tube must therefore not consist of two tubes joined by a rubber stopper as I have heretofore used them in ammonia determinations but must be connected by the glass blower. Eimer and Amend have made me some excellent tubes suitable for this purpose. Finally no one should attempt to use the method on unknown solutions or urines until he has satisfied himself that he can get accurate figures with known acetone solutions. Such solutions can be made and standardized in a few minutes by direct titration with the iodine and thiosulphate solutions. Ten c.c. of pure acetone diluted up to one-fourth of a liter and twenty c.c. of this solution diluted to half a liter makes a suitable test solution of acetone.

The addition of an excess of sodium chloride as described above is important and should not be omitted. Acetone is insoluble or at least very little soluble in saturated sodium chloride solutions.

I am now investigating the acetone and diacetic acid contents of diabetic urines by the help of this method. Most such urines even when rich in diacetic acid contain surprisingly little acetone.

73 (216)

On magnesium and contractile tissues.

By **Percy G. Stiles.**

[*From the Biological Department of the Massachusetts Institute of Technology.*]

The experiments reported extend and confirm the findings of Meltzer and Auer. Magnesium is found to have a direct inhibitory effect on automatic tissue (plain and cardiac muscle) and a depressing effect upon the irritability of the non-automatic striped muscle.

This influence is slow to wear off after the application but seems generally to favor the later activity of the muscle — in other words, it is conserving in character. Magnesium appears to be the element to which we may look with most reason when seeking an agent that shall suspend katabolic changes without permanently damaging living structures. It is clearly less hurtful than potassium in like concentration. Comparison of magnesium with potassium shows that the former is not so distinctly the antagonist of calcium as is the latter. It also seems probable that the power to mediate vagus inhibition which Howell fixed upon potassium is a unique property of that element and not shared by magnesium.

74 (217)

On the extracellular and intracellular venom activators, with special reference to lecithin, fatty acids and their compounds.

By **HIDEYO NOGUCHI.**

[*From the Rockefeller Institute for Medical Research.*]

Calcium chloride stops venom hemolysis caused in the presence of oleic acid or soluble oleate soaps, but not that induced by lecithin. In the majority of serums, including those of man, horse, guinea pig, rabbit, cat, rat, hen, pigeon and goose, there exist greater or less amounts of venom activators, and they can be completely inactivated by calcium chloride. Judging from the fact that lecithin in an available form is not affected by this salt it is not likely that these serums owe their venom activating property to lecithin. As these activators are also extractable with ether they probably are nothing else than certain fatty acids, and, probably, soluble soaps. Dog's serum is an exception to this, and contains, besides fatty acids and soaps, also activators of the nature of lecithin, for calcium chloride fails to stop completely its venom activating property. This lecithin-like activator is not extractable with ether, but is precipitable by half saturation with ammonium sulphate together with the serumglobulin. While the serum globulin falls out as a precipitate during dialysis this activator remains in the solution, from which a large percentage of lecithin is extractable with warm alcohol. In many respects this appears to be a protein compound of lecithin and possibly is identical with

Chabrie's albumon. This peculiar protein compound of lecithin seems to be absent from the majority of normal serums. Chabrie's albumon develops in any serum heated to coagulation, and renders all serums equally venom activating. Ovovitellin is another form of protein compound containing lecithin in available form for venom. On the other hand, pure serum globulins or serum albumins are not venom activating, notwithstanding their content of alcohol-extractable lecithin. Non-activating serum can be made activating by adding small quantities of oleic acid or oleate soaps.

The degrees of susceptibility of corpuscles are parallel to the amounts of fatty acids which they contain. The absence of fatty acids is associated with total insusceptibility of the corpuscles to the hemolytic agent of venom. The amounts of lecithin extractable from corpuscles are about the same in different bloods and bear absolutely no relation to susceptibility. The addition of adequate amounts of calcium chloride stops venom hemolysis with washed corpuscles of susceptible species. A previous addition of a small amount of lecithin annuls protection by this salt. A small amount of oleic acid or soluble oleate soap, which is insufficient to produce hemolysis alone, can render the corpuscles of insusceptible species hemolyzable by venom. An oily substance can be extracted with ether from the stoma of susceptible corpuscles, but not from the insusceptible varieties. This oily mass is venom-activating but contains no lecithin.

75 (218)

On the influence of the reaction, and of desiccation, upon opsonins.

By **Hideyo Noguchi.**

[*From the Rockefeller Institute for Medical Research.*]

The non-specific antiopsonic property of certain neutral salts and of lactic acid has been studied by Hektoen and his co-laborers, but the relation of the reaction to the opsonic activity of serum has so far escaped attention. The results of my experiments show that opsonins are most active in neutral reaction. For this the serums of the dog, ox, pig and rabbit were employed. Lacmoid was used as an indicator. The technic was essentially the same as Wright's.

Human leucocytes and staphylococcus aureus were used and the time of incubation was thirty minutes, at 37°C. An alkalinity of the fluid exceeding 1/20 normal KOH prevented the occurrence of opsonization. An acidity of 1/30 normal HCl was sufficient to stop the opsonic function of the serum. Neutralization of the excessive alkalinity or acidity caused reappearance of opsonic activity. On the other hand, an alkalinity or an acidity approaching that of the normal alkali or acid produced a condition of irreversibility of the inactivation. The opsonic index estimated in the usual alkaline reaction of normal serum is far lower than that in a neutral medium.

The high stability of opsonins against desiccation and the high thermostability of dried opsonins are very striking. Almost no reduction of opsonic strength is experienced after a serum is completely dried at 23°C. within a few hours. In dry state opsonins are well preserved even after two years. Dried serums of crotalus, ox and horse gave positive results in this regard. The temperatures of 100°, 120°, 135° and 150°C. do not destroy opsonins in the dry state. At 150°C. the serum becomes difficult to dissolve, but opsonins may still be detected in it.

Complements withstand desiccation and dry heat in a manner similar to the resistance of opsonins.

76 (219)

On decomposition of uric acid by animal tissues.

By **P. A. LEVENE** and **W. A. BEATTY**.

[*From the Rockefeller Institute for Medical Research.*]

About two years ago in a communication before this society we indicated the most favorable conditions for the decomposition of uric acid by tissues.

Several papers on the same subject have recently been published in which it was demonstrated that uric acid may suffer decomposition through the action of tissue extracts in the presence of dilute sodium bicarbonate.

This confirms the results in our previous paper. In our recent work uric acid was subjected to the action of splenic pulp in the presence of 2 per cent. ammonium hydroxide and 2 per cent. acetic acid.

Under both conditions uric acid was decomposed to the amount of 50 per cent. of that present. Allantoin was one of the decomposition products. In the first communication mention was made of the fact that basic substances were formed in the process of dissolution.

77 (220)

On the diuretic action of thymin.

By **P. A. LEVENE.**

[*From the Rockefeller Institute for Medical Research.*]

In work done by Sweet and the writer the observation was made that the administration of thymin to a dog with an Eck fistula caused marked diuresis. The experiments were continued this year on a dog with an Eck fistula prepared by Dr. Carrel. The dog had been kept on a purin free diet many weeks before the experiment was begun. For three weeks preceding the experiment the water consumed by the dog and the urine eliminated were carefully measured. It was noted that administration of thymin was followed by marked diuresis.

78 (221)

On lysinglycyl obtained in the tryptic digestion of egg albumen.

By **P. A. LEVENE** and **W. A. BEATTY.**

[*From the Rockefeller Institute for Medical Research.*]

In the process employed by the writers a year ago for preparing the peptid prolinglycyl, a substance was produced from egg albumen, which on further cleavage yielded only lysin and glycocoll. The substance could not be crystallized. It is a noteworthy fact that peptids of the hexon bases obtained by Fischer and Suzuki synthetically also failed to crystallize.

Twenty third meeting.

New York University and Bellevue Hospital Medical College. May 22, 1907. President Flexner in the chair.

79 (222)

The osmotic pressure of colloidal solutions and the influence of electrolytes and non-electrolytes on such pressure.

By **RALPH S. LILLIE.**

[*From the Physiological Laboratory of Johns Hopkins University.*]

Determinations were made of the osmotic pressure of gelatin and egg albumin; the colloids were used (1) in approximately pure solution, and (2) after the addition of various electrolytes and non-electrolytes to the colloidal solution; in this case the substance used was added in the same concentration to the outer fluid of the osmometer so as to pervade the entire system on both sides of the membrane in uniform concentration. The osmotic effects observed under these conditions can be due only to the colloid and not to the added substance. The colloidal solution is found, however, after the addition of an acid, alkali, or neutral salt, to exhibit an altered osmotic pressure, the degree of alteration varying with the nature and concentration of the added electrolyte. Non-electrolytes are found to have no appreciable influence on the osmotic pressure of these colloids.

The osmometer employed is constructed as follows: The membrane is composed of a moderately thick film of nitro-cellulose (celloidin or gun cotton) and is of the form and capacity of a 50 c.c. round bottomed flask; it is made by coating the interior of such a flask with a thin film of a 10 per cent. solution of celloidin in equal parts of alcohol and ether, and then removing the solvent by evaporation and bathing in hot water. Such membranes are strong and inextensible, readily permeable to crystalloids and water, and (if of the proper thickness) almost impermeable to the above proteids. The manometer is a straight narrow glass tube passing through a rubber stopper which is bound by an elastic

band into the neck of the flask-shaped membrane. The latter, after introduction of the colloidal solution, is immersed in a definite volume of the pure solvent (water, or water plus electrolyte used) contained in a battery jar; the jar is covered by a glass plate to prevent evaporation. The manometer tube is clamped in a vertical position. The height to which the column of fluid rises is a measure of the osmotic pressure; a constant height is reached in eighteen hours or less; pressure readings thus obtained may easily be translated into millimeters of mercury, if the specific gravity of the solution within the membrane is known.

The following general results have been gained. Non-electrolytes (sucrose, dextrose, glycerin, urea) have little or no influence on the osmotic pressure of the above colloids. Electrolytes, on the other hand, invariably produce a marked alteration. For example, the osmotic pressure of gelatin is greatly increased by the addition of small quantities of either acid or alkali. Thus in one experiment a 1.5 per cent. solution of gelatin gave a pressure of 8.4 mm. Hg; the same solution with the addition of HCl to $n/410$ concentration gave a pressure of 41.1 mm. Hg; with $n/410$ KOH it gave 26.3 mm. Hg. Egg albumin differs from gelatin in showing a *depression* of osmotic pressure in presence of acid or alkali. In all cases neutral salts *depress* osmotic pressure; in general there is seen a parallelism between the effectiveness of the salts as precipitants and their action in lowering osmotic pressure. The action is less pronounced — for equimolecular concentrations —with alkali metal salts than with salts of alkali earths; heavy metal salts depress to a still greater degree. A typical series with 1.5 per cent. egg albumin and the following potassium salts gave this result: (1) control: 22.6 mm. Hg; (2) same solution + $m/24$ KCl: 4.6 mm.; (3) $m/24$ KBr: 5.0 mm.; (4) KI: 5.4 mm.; (5) KNO_3: 5.7 mm.; (6) KCNS: 6.0 mm.; (7) K_2SO_4: 4.0 mm. The action thus varies with the nature of the anion; in general the order of decreasing effectiveness of anions is somewhat as follows: $SO_4 < Cl < NO_3 < Br < I < CNS$. This order coincides with that found by Hofmeister and Pauli for the action of anions in changing the aggregation-state of proteid solutions. $M/96$ $CaCl_2$ in a typical experiment depressed the osmotic pressure of a 1.5 per cent. albumin solution from 18.8 mm. Hg (control)

to 5.4 mm. Other alkali earth chlorides showed similar action. Heavy metal salts, short of the concentrations that cause precipitation, are still more effective as depressants.

80 (223)

Hemolysis in eclampsia.

By **JAMES EWING.**

[*From the Department of Pathology, Cornell University Medical College, New York City.*]

There are several reasons suggesting that a hemolytic agent of placental origin may be of essential importance in eclampsia. The occurrence of methemoglobinuria, the possible relation of the hepatic thromboses to hemolyzed red cells, the resemblance between the eclamptic lesions and those produced by the injection of eclamptic serum or of immune hemolytic serum in rabbits, the possible origin of the eclamptic toxin from the placenta which normally possesses a hemolytic ferment, the marked hypertrophy and desquamation of the syncytium at term and during labor, and the relief of the symptoms in many cases as soon as the placenta is removed, all tend to indicate a hemolytic agent derived from the placenta as a factor in the disease.

In order to obtain some information regarding this subject I examined the placenta in fifteen cases of eclampsia, and the circulating blood and the viscera of several fatal cases for evidence of hemolysis. If any marked degree of hemolysis had occurred during life one would expect to find evidences of it in fresh emulsions of placental blood made shortly after delivery. Spreads of the blood on glass slides were also examined for evidence of agglutination and hemolysis, and sections of the placenta hardened in Orth's fluid were examined. Several normal placentas were first tested, and in these no evidences of hemolysis appeared immediately or after three to fifteen hours in the thermostat. In spreads and sections of normal cases the red cells often appeared moderately clumped without being fused. In only one of the eclamptic placentas was evidence of hemolysis secured, and this occurred in a fatal case in which, also, similar evidence was found in the uterine, portal and hepatic veins. The urine was bloody.

This patient had received a large salt infusion during the convulsive period. In two other fatal cases hemolysis was found only in emulsions made from the spleen, but not in the hepatic, portal, or uterine veins, or in the placenta. In a fourth fatal case with bloody urine and extensive hemorrhages in the brain, liver, and peritoneal cavity, 300 c.c. of blood were drawn from the arm during life. The serum was entirely unstained by hemoglobin.

The blood of the placenta mixed with fetal blood, or with extracts in salt solution of liver and kidney, failed to hemolyze.

The observations indicate that the eclamptic toxin is not a hemolytic agent derived from the placenta, and that hemolysis is not necessarily associated with the lesions of the viscera. Semb's observations in which he demonstrates visceral lesions strongly resembling those of a hemolytic serum, cannot be accepted as evidence of a specific eclamptic toxin. Histological study of the liver of eclampsia indicates that the characteristic lesions consist in fibrin thrombi and not in agglutination and hemolysis of red cells, and that when hemolysis occurs it results from the products of degeneration and necrosis of endothelial and hepatic cells. It is therefore probably an entirely secondary factor in the disease.

81 (224)

Glycocoll nitrogen in the metabolism of the dog.

By J. R. MURLIN.

[*From the Physiological Laboratory of the New York University and Bellevue Hospital Medical College.*]

While attempting to explain the behavior of gelatin in metabolism it occurred to the writer that much significance might be attributed to its high content of glycocoll. It is well known that the nitrogen of gelatin is not ordinarily retained in the body but appears quantitatively in the urine, chiefly as urea. But when fed with meat and abundance of carbohydrate it is possible to establish nitrogen equilibrium near the fasting level, if two-thirds of the total quantity of nitrogen fed is present in proteid-free gelatin and only one-third present in the meat.[1] Would glycocoll, if fed in the same way, behave as does gelatin?

[1] Murlin: This journal, 1905, ii, p. 38.

v. Brügsch and Hirsch fed 20 gm. of glycocoll[1] to a fasting woman on the twelfth day of her fast and observed that all of its nitrogen appeared in the urine as urea. Samuely[2] had likewise observed this fate (chiefly) of glycocoll nitrogen when glycocoll was added to meat and other foodstuffs in the diet of dogs suffering from artificial anemia. But Lüthje[3] reports a nitrogen retention, with asparagin and glycocoll as the only sources of nitrogen, provided carbohydrates are fed freely at the same time. He thinks there may be a synthesis of the amino acids with carbohydrate and the formation of an "amino sugar," which escapes the destructive processes of the body.

It has appeared in my experiments with gelatin that the power of the body to conserve its nitrogen supply is stronger the lower the proteid condition of the animal at the time of feeding. For the purpose of testing the power of retaining glycocoll nitrogen therefore, I prepared the dogs by subjecting them to long periods of fasting or under-nutrition. For example, a dog weighing in good condition 6.5 kg. fasted for 13 days, during which the weight fell to 4.8 kg. Then for two weeks more he was kept in under-nutrition as regards proteid, for the purpose of a gelatin experiment. At the end of the month the weight had been reduced to 4.2 kg. The total output of nitrogen on the last day of a fasting period at this time was 1.247 gm. By feeding for a period of 5 days, 6.4 gm. of proteid-free gelatin and supplying over 100 cal. per kg. of energy (chiefly in the form of carbohydrates), the output of nitrogen was reduced to 0.406 gm. Ten days later on a diet containing 0.491 gm. of nitrogen in the form of beef heart and 150 cal. per kg. (weight still 4.2 kg.), the dog was almost in nitrogen equilibrium (— 0.02). To this diet were then added 5 gm. of glycocoll containing 0.951 gm. nitrogen, bringing the total nitrogen ingested up to 1.442 gm. The diet was continued for five days, on four of which there was nitrogen retention — a total for the period of 0.257 gm. But on the day following when the glycocoll was dropped and when there should have been nitrogen equilibrium, as there was previ-

[1] v. Brügsch and Hirsch : Zeitschr. f. ex. Path. u. Ther., 1906, p. 638.

[2] Samuely : *Deutsch. Arch. f. klin. Med.*, 1906, p. 220.

[3] Lüthje : *Pflüger's Arch.*, cxiii, summary p. 604; also Kongress f. inn. Med., 1906, p. 440.

ous to the glycocoll feeding, there was a loss of 0.435 gm. N. It is believed that this loss includes the glycocoll nitrogen retained temporarily.

A second dog weighing in good condition 5.4 kg. fasted for 10 days during which the body weight fell to 4.6 kg. The nitrogen output on the last fasting day was 1.697 gm. For five days immediately following this, 1.496 gm. of nitrogen were given, two-thirds of it (1.006 gm.) in the form of very pure gelatin and one-third (0.490 gm.) in the form of beef heart. A total energy supply of 130 cal. per kg. (chiefly carbohydrates) was maintained. On the fifth day there were 1.55 gm. N in the urine. On the next day the gelatin N was replaced by glycocoll N and, singularly enough, the nitrogen output in the urine was exactly 1.559 gm. This, however, is probably a mere coincidence and is not to be interpreted as showing that glycocoll N exerts the same sparing effect on the body proteid as gelatin, for on the second day with glycocoll, the nitrogen in the urine rose to 1.898 gm.

A fasting period of five days was next introduced, the nitrogen in the urine on the last day being 1.288 gm. For three days thereafter 7 gm. of glycocoll, containing 1.332 gm. N were given, and the total energy supply was made up with carbohydrates and a small quantity of fat (10 gm.) to 140 cal. per kg. The nitrogen loss represented by the urine alone on the three days was 0.125, 0.280 and 0.674 gm. respectively. Then the glycocoll was dropped and the carbohydrates with a small quantity of fat were continued for two days. The nitrogen in the urine for these days was 0.987 and 0.713 gm. respectively. A third day would probably have reduced it still more, since as Landergren [1] has shown, it is possible to reduce the nitrogen output of a man to about one-third of what it would be in fasting, by ingestion of carbohydrates alone. While, therefore, there is an evident benefit, as regards waste of nitrogen, conferred by the glycocoll while it is being ingested, the nitrogen which it conserves is rapidly eliminated after the feeding period. It is possible that this nitrogen is retained temporarily in the form of glycocoll itself, since as shown by Parker and Lusk,[2] the amount of glycocoll which may be removed by combination with

[1] Landergren: Review by Hammarsten, *Maly's Jahresber.*, 1902, p. 685.

[2] Parker and Lusk: *Amer. Journ. of Physiol.*, 1900, iii, p. 472.

benzoic acid given to rabbits is greater on the first day of the administration during a fasting period than on subsequent days. Whether the glycocoll is combined with carbohydrate as an amino-sugar, as Lüthje imagines, or not, it is evident from the several experiments that no permanent synthesis takes place. Glycocoll, therefore, behaves in much the same way in metabolism as does gelatin.

82 (225)

An hydrodynamic explanation of mitotic figures.

By **ARTHUR B. LAMB** (by invitation).

[*From the Havemeyer Chemical Laboratory, New York University.*]

The distinctly polar arrangement of the chromatin substance about the astral centers in dividing cells, combined with the pronounced curvature of the astral rays and of the spindle fibers, have demanded the assumption of some polar force as universally operative. On such an assumption it is of course necessary to assume further that astral centers represent either opposite or like poles. On the alternative of opposite poles, we should expect, with any force so far proposed, a configuration of astral rays simulating that of iron filings between *opposite* magnetic poles, coupled with a mutual *attraction* of the astral centers. On the other alternative, we should similarly expect a configuration of astral rays and spindle fibers simulating that of iron filings between *like* magnetic poles, coupled with a mutual *repulsion* of the astral centers. Actually, we have neither of these conditions, but instead, a configuratian like that of iron filings between *opposite* magnetic poles *and at the same time an apparent repulsion between the astral centers or the centrosomes.*

This is not the case with the forces of attraction or repulsion existing between bodies oscillating or pulsating in a fluid medium. More specifically, if two spheres are pulsating synchronously and in opposite phase, or oscillating synchronously and in the same phase, they will repel one another, *but at the same time the field between them will simulate the configuration of iron filings between opposite magnetic poles.*[1]

[1] See Bjerknes' text-book, "Hydrodynamische Fernkräfte," J. A. Barth, Leipzig, 1902.

If then we assume that the centrosomes are pulsating in opposite phase, or better, oscillating in the same phase, we will obtain the desired repulsion and at the same time have a configuration like that actually observed.

The configuration taken by the chromosomes is explicable on the same grounds. Indeed, it is not necessary to assume any independent motion on their part, but simply to consider it an induction phenomenon. The tri- and multi-polar spindles are also better explained on these hydrodynamic grounds than on previous assumptions.

The foregoing explanation is, of course, pure hypothesis, with no support other than the facts it seeks to explain. There is, however, nothing inherently impossible in it, and it may provoke fresh observation and new ideas.

83 (226)

Transfusion experiments in dogs showing artificially implanted tumors.

By **GEORGE W. CRILE** and **S. P. BEEBE.**

[*From the Department of Experimental Pathology, Cornell University Medical College, New York City.*]

Direct transfusion of the whole blood from immune dogs to dogs with actively growing, artificially implanted tumors has been carried out upon a series of six animals. The operative method of this transfusion is the same as has been used by one of us in a large series of experiments previously reported in the proceedings of this society.[1] In the first set of three, sufficient time has elapsed to determine the outcome, and we give below brief data of each experiment in this series.

I. Dog 116. Planted Jan. 7, 1907. Tumors were first seen on Feb. 20; continued to grow slowly. March 20, transfusion experiment — dog was bled 400 c.c. and immediately transfused with 550 c.c. of blood from dog 244, in which implantation had occurred on Jan. 18th; tumors were first noticed on Feb. 6th, and had continued to grow until Feb. 20th, when they began to regress. Regression complete March 7th. Three days after transfusion,

[1] Crile and collaborators: This volume, pp. 6, 64, 65 and 67.

dog 244 was again planted with tumor. Four plants were made with positive results in three and tumors are growing at the present time. The immunity which dog 244 possessed as a result of the previous growth and regression of the tumors could not have been very marked. The effect of this transfusion upon tumors of dog 116 was negative, since they continued to grow until the death of the animal in a cachetic condition four weeks later.

II. Dog 125. Weight 13 kilos. Tumors were planted Dec. 6th. All plants grew and continued to increase in size until the day of transfusion, March 20. On this day the dog was bled 500 c.c. and immediately transfused with the same quantity of blood from Dog 163. The latter animal had previously grown these tumors, but they had completely regressed. Repeated implantations failed to give tumor growth, and although the animal had the mange and was in poor physical condition, he was used for the donor in the transfusion. Following the bleeding and transfusion the tumors of dog 125 became softer and began to regress. The regression continues at the present date. One tumor has entirely disappeared and the others have subsided. There remains about one eighth of the tumor tissue present at the time of transfusion. A metastasis in one of the inguinal lymph nodes has appeared since the transfusion. Before the transfusion four plants were made on the back. These have developed since the transfusion and are now growing slowly. There is therefore in this animal at the present time one set of tumors regressing and another set slowly growing.

III. Dog 133. Weight 17 kilos. Tumors planted Jan. 31st; first growth noticed Feb. 13th, and continued active until day of transfusion. March 20th, bled 600 c.c and transfused 1500 c.c. from dog 289. The latter animal was 19½ kilos in weight, in very good physical condition and naturally immune to the tumor. Following this transfusion, which was the largest and of the best quality that any animal in this series received, the tumors of dog 133 began to regress immediately, and at the present time the regression is complete.

We merely wish to present the facts and do not care to indulge in a discussion regarding immunity to tumors or the bearing which these experiments have upon current theories.

84 (227)

Transplantation of the thigh from one dog to another.

By **ALEXIS CARREL.**

[*From the Rockefeller Institute for Medical Research.*]

The first attempts at transplanting a limb from one animal to another were made last year in the University of Chicago by Guthrie and myself. No definite results were observed because of infection or the breaking of the bone suture.

Lately the transplantation of the thigh from one dog to another was tried again with an improved technique.

On April 23, 1907, at 9.50 a. m., a medium-sized dog was killed with chloroform. At 10.20 a. m. the left thigh of the cadaver was amputated just below its middle part, perfused with Locke's solution and placed on a table of the laboratory, the temperature being 88–90° F.

At 11 a. m., a medium-sized bitch was etherized, her left thigh amputated and immediately replaced by the thigh of the dead dog. The reconstruction of the thigh began by the suture of the bone, the adductors and quadriceps. Then the femoral vessels were united and the circulation re-established at 1 p. m. The operation was completed by the suture of the nerves, muscles, aponeuroses and skin, and the limb placed in a plaster of Paris apparatus.

On April 23, 24 and 25 the animal remained in good condition and walked on her three normal feet. The transplanted limb was warmer than the normal one and its circulation very active. On April 26, she appeared to be sick. There was a phlegmon of the thigh. Incisions were made in Scarpa's triangle and on the transplanted limb, which was warm. Hemorrhage of red blood occurred from the incisions in the transplanted limb.

During the succeeding days, the circulation of the limb remained active, the foot became swollen and the general condition of the animal declined. On May 1, a large abscess was detected near the pelvis and opened. A small incision having been made on the foot of the transplanted limb, hemorrhage of red blood occurred. The general condition of the animal was very low. On May 2, the animal died of septicemia.

Then, it was found that the lumen of the femoral vessels was

free of thrombus, and the intima, smooth and glistening. There was no deposit of fibrin on the lines of suture. In spite of the infection, the union of the vessels was excellent. The skin and the muscles were cicatrized and the ends of the femur firmly united by the ligature.

85 (228)

The bacteriotherapy of leprosy.

By **PAUL G. WOOLLEY** (by invitation).

[*From the Government Serum Laboratory, Phrapatoom, Siam.*]

That a given organism either cannot be grown outside the body, or can only be grown with great difficulty and uncertainty, would appear, at first sight, to offer an insuperable obstacle to the development of any method of therapeutic vaccination, — vaccination, that is, during the course of a disease, by inoculations with the specific bacteria, or their products, — such as has been practiced by Koch in connection with tuberculosis, and by Wright to arrest suppurative and other conditions. Preëminent among microbes belonging to this category is the leprosy bacillus : the difficulties in the way of gaining adequate growths of this organism have thus far prevented the development of any bacteriotherapeutic means of treating the disease due thereto.

A possible method of overcoming the obstacle has suggested itself to me ; and I am already testing it. But in Siam, the number of suitable cases presenting themselves is not great. The value of the method can only be determined by noting the results gained in a relatively considerable number of cases ; hence it has seemed to me advisable to describe it in the hope that others having fuller opportunities may be induced to test the procedure and its value. My somewhat remote station is against a familiarity with the most recent literature : to my knowledge the method has not hitherto been published, and is original. The nearest approach to it, that of *preventive* vaccination against black-leg by means of the desiccated spore-bearing muscle tissue of a previous case, differs in many important particulars.

Briefly, it seemed to me that lacking pure cultures for the purpose, I might make the leprosy patient serve as his own culture medium. It is well known how abundant are the bacilli in the

lepra nodule. I thus sought a leper who would, for a small inducement, place himself under treatment and succeeded in gaining a beggar for what thus became in truth an *experimentum in corpore vili*, for he is an advanced and wretched case of the tubercular form of the disease. I excised a nodule from his arm; found it very rich in bacilli; ground it with sand and salt solution; centrifugalized; heated to 65–70° C. for fifteen minutes, and added enough 5 per cent. carbolic acid to make a suspension containing 0.5 per cent. of the acid. This suspension is rich in bacilli; of it I make at intervals subcutaneous inoculations of 0.01 ccm., the intervals depending on the general condition of the patient. Experience with the more exact methods possible with the analogous disease, tuberculosis, indicates that minimal inoculations of the dead bacilli must be continued over a long period before a genuine arrest is attained; even, therefore, with the most favorable outcome, I cannot expect to record the results of this treatment for months to come; on the other hand, the case was already so advanced when inoculation was begun that I am not sanguine of any pronounced favorable results. I would only repeat that the method appears to deserve publication, that others with fuller opportunities may test and, it may well be, improve upon it.

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Direct silver staining of spirochetes and flagellated bacteria.

By SIMON FLEXNER.

[*From the Rockefeller Institute for Medical Research.*]

The discussion of the nature of the structure now called spirochete (Treponema) pallida — whether a microorganism or some histological elements — led me to try to effect the silver staining directly upon smear preparations prepared from serum exudates obtained from syphilitic lesions. While engaged unsuccessfully in this endeavor, Stern[1] of Prag published a simple method for staining the spirochetes directly with silver nitrate. When the deposit of silver presents a metallic sheen, the impregnation is regarded as sufficient. I have found the method very simple and sufficient; but I have obtained better results from long (3–4 days)

[1] Stern: *Berl. klin. Woch.*, 1907, xliv, 400.

than from short (1–2 days) exposures. The length of exposure required will depend somewhat upon the weather (strength of light) and the thickness of the spread. Moderately heavy spreads have given me better results than thinner ones, and impression preparations better than smear preparations. In the shorter exposures, some of the spirals will show uniform breaks between the curves which may be attributed to the relation existing between spirochete and medium, the more superficial curves being first impregnated. By longer exposure, the broken spirals are made complete, probably by impregnation of the deeper-lying curves. Disagreeable precipitation is not present on the serum-covered film, but occurs on the adjacent uncovered glass. The direct demonstration of silvered spirochetes may be taken as a concluding proof of the microorganismal nature of the spirals.

Other spirochetal organisms, from the buccal cavity, etc., may be silvered by this method, and bacteria may also be silvered. In a few comparative tests which I made, the degree of impregnation was greatest with the pallida. Whether this is to be accounted for by elective affinity or difference of medium in which the organisms were embedded I cannot say. In the course of these examinations, I came across examples of flagellated bacteria from the buccal cavity in which the flagella were distinctly silvered. I attempted to stain the flagella of certain bacteria — B. typhosus, paratyphosus, pyocyaneus, hog cholera — from pure cultures, but unsuccessfully. The terminal cilia of the pallida appeared not to be stained by the silver.

I have observed instances in which the silvered films showed many more spirochetae pallida than the corresponding preparations stained by Giemsa's or Proca's methods. I shall mention one instance in which in preparations from a macerated syphilitic fetus, the number of pallida brought out by the silver impregnation was very large, while very few spirals were found in the Proca stained films from the adrenal gland and skin. The silvered film from the skin showed small groups of pallida and a colony-like mass such as I had not observed before in any film preparation.

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On the bacterial production of skatol and its occurrence in the human intestinal tract.

By **C. A. HERTER.**

[*From the Laboratory of Dr. C. A. Herter, New York City.*]

Observations upon skatol produced in the course of putrefactive decomposition are at present few and imperfect. This is due largely to the difficulties incidental to the certain recognition of this substance when present in small amounts. By means of a method described by Herter and Foster it is possible to detect the presence of very small quantities of skatol in a putrefactive mixture, to separate skatol from indol and to estimate the quantity of skatol present. This method is based on the use of β-naphthoquinone sodium monosulphonate and para-dimethyl-amidobenzaldehyde (Ehrlich's aldehyde). By means of this method, studies have been made with a view of discovering what organisms are chiefly concerned with the production of skatol, and many observations have been made upon the presence of skatol in the human intestinal tract. A large number of facultative and strict anerobic organisms have been studied with respect to their ability to form skatol. The anerobes *B. putrificus* (strain isolated by Bienstock) and one strain of the bacillus of malignant edema (obtained from Prof. Theobald Smith) were found to produce skatol in peptone bouillon, although it was not possible to determine the conditions under which skatol could be regularly obtained through the action of these bacteria. It was found that skatol is rarely present in the intestinal tract except in conditions of disease associated with intestinal putrefaction. Usually skatol is associated with indol in such conditions, although there are instances in which the intestinal contents contain little or no indol, but, relatively speaking, considerable skatol. This has been observed heretofore only in putrefactive processes associated with pronounced clinical manifestations.

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A spirochete found in the blood of a wild rat.

By **W. J. MACNEAL.**

[*From the Bacteriological Laboratory of the University of West Virginia.*]

Of thirty nine wild rats (*Mus decumanus*) caught here at Morgantown one has shown a minute actively motile spiral organism in the blood. It is present in very small numbers and careful search with high magnification is necessary to detect its presence. In freshly drawn blood it appears as an elastic spiral rapidly darting about, as often with one end forward as the other, forth and back, rotating on its long axis as it goes. The movement is frequently too rapid for the eye to follow. The spiral turns appear quite permanent. At times a lashing movement of the whole body is seen but the organism straightens out quickly to its former shape. When caught among blood cells it jostles them about in a lively fashion, while it is itself invisible. This seems to be due to these flexuous movements of the whole organism. Actual contact of the spiral appears to be necessary before the blood cells are moved, which suggests that flagella are absent or too slender to make a visible impression on an erythrocyte.[1] The organisms are difficult to measure in the living condition but the greatest length observed is about 5 μ. Much shorter forms are recognizable in the fresh preparation, though harder to see on account of the more active movement. The refractive index of the parasite is not very great.

The parasite stains readily by the various modifications of the Romanowsky stain, and very intensely by the rapid method which I have recommended for clinical staining of *Spirochæta pallida*.[2] It takes a uniform deep violet red color. The measurement of a number of individuals shows a marked variation in length, the shortest forms, consisting of one and three quarters turns or nodes, having a length of 1.75 μ; the longest, consisting of three and

[1] Since this communication was written a long slender whip-like process extending from each end of a spiral has been clearly demonstrated. These are interpreted as locomotive organs.

[2] MacNeal: *Journal Amer. Med. Assn.*, Feb. 16, 1907.

one half turns, being 3.55 μ long. Rather infrequently spirals 3.75 to 4.00 μ in length are seen, and these present central constrictions suggesting transverse division. From the striking variation in length also, this would appear to be the mode of multiplication. All intermediate lengths are seen. The width of the filament is approximately 0.25 μ, the gross width of the coil about 0.65 μ. The length of a turn or node (crest to crest) is 1.0 to 1.5 μ, fairly constant, but indicating some longitudinal extensibility of the coil. By raising the plane of focus above the stained parasite the upper segments of the turns are seen more clearly than the lower. They run forward from left to right. In lower focus the lower halves are the more clearly defined, and are seen to extend forward from right to left. The spiral therefore corresponds to the ordinary right hand screw, turning clockwise as it proceeds from a given point. This seemed to be true of all the individuals examined, though some were too much flattened against the glass to manifest an appreciable difference in focus.

The infection is readily transferred to other wild rats by intraperitoneal injection of a very small drop of infected blood in normal salt solution. In many cases not more than ten or twenty parasites could have been present in the injection, yet, so far, the wild rats have always developed the infection. Of seven wild rats inoculated, the parasites were first detected in the blood of one on the fifteenth day, in one on the eleventh, in one on the twelfth, in three on the tenth and in one on the seventh day. The last mentioned was a small rat and received a relatively large dose, one fourth cubic centimeter of defibrinated blood and one-half cubic centimeter of a thick suspension of the organs in salt solution, from a rat showing one spirochete in every four fields of blood film. The parasites never become very numerous and disappear in from one to nine days. This apparent recovery is then followed by repeated relapses. The parasites may become more numerous in the blood during the relapse than in the primary invasion. Neither a certain recovery nor a fatal result has, as yet, been observed.

White rats are susceptible, with an incubation period of four to eight days, according to the dose employed.

The house mouse (*Mus musculus*) is apparently more resistant.

So far only one has been successfuly inoculated. A relatively large dose was injected and the incubation period was twelve days. Three other mice were observed for six, ten and twelve days, respectively, after inoculation without showing a parasite.

Similar spirochetes have been described by Carter (in rat), Lingard (in bandicoot, *Mus giganteus*), by Nicolle and Comte (in bat), by Wenyon and by Breinl and Kinghorn (in house mouse); all these in the circulating blood. Borrel and Gaylord have described spiral organisms in mouse carcinomata, and one of the forms found by Borrel has been shown by Wenyon to be identical with his *Spirochæta muris* found in the blood of mice. Morphologically the parasite found here in the rat is apparently identical with this one of Borrel and Wenyon. Its behavior in animals is somewhat different. Therefore, I tentatively suggest for it the name *Spirochæta muris*, var. *Virginiana*, following the principle suggested by Calkins.[1] Its specific relation to that organism must be left for further work to determine.

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Experimental ligation of splenic and portal veins, with the aim of producing a form of splenic anemia.

By ALDRED S. WARTHIN.

[*From the Pathological Laboratory, University of Michigan.*]

From the pathological study of four cases of splenic anemia showing partial or complete obstruction of splenic or portal veins due to old thrombophlebitis, the writer was led to believe that the splenic enlargement (fibrosis) and the clinical picture of splenic anemia might be produced experimentally in animals. During the last two years he has carried on a series of observations upon dogs whose splenic veins had been ligated at varying distances from that organ. Briefly, the results have been as follows:

In dogs examined from one week to three months after the operation the spleen was found greatly enlarged, firm and dark in color. This enlargement reached its extreme about four weeks after the ligation.

[1] Calkins: *Journal of Infectious Diseases*, April, 10, 1907.

In dogs examined after three months the spleen was found to be diminished in size, paler and firmer. In those examined one year after ligation of the splenic veins the organ was found to be greatly atrophic and fibroid, in two cases completely separated into small islands or lobes of splenic tissue, each lobe having a separate vein running into the gastro-splenic omentum, and anastomosing with veins from the stomach. Such a collateral circulation was found established in all cases.

All animals with splenic atrophy become very fat. Hyperplasia of the prevertebral hemolymph nodes was noted. There was a slight anemia, the hemoglobin being reduced to a greater degree than the red blood cells. No lasting changes in the white cells were observed. Microscopically the spleen showed a lymphoid atrophy, relative increase of stroma and excessive pigmentation.

These experiments would indicate that obstruction of the splenic veins of dogs by ligation is not followed by a fibroid hyperplasia of the spleen but by a partial atrophy. A more or less complete venous collateral circulation is always produced. The picture of splenic anemia as seen in man can not, therefore, be reproduced in the dog, by an obstruction to the venous outflow from the spleen.

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An experimental control of Fischer's attraxin-theory.

By **C. SNOW.** (Communicated by **ALDRED S. WARTHIN.**)

[*From the Pathological Laboratory, University of Michigan.*]

Fischer recently reported from Ribbert's laboratory[1] that by injecting a solution of Scharlach R, Sudan III or Indo-phenol in olive oil under the skin of the ears of rabbits he was able to get an epithelial proliferation which was not to be distinguished histologically from a squamous-celled carcinoma in man. He was not able to get this result with other substances acting as irritants, and therefore assumed the existence of specific bodies — attraxins — in the injected solution, which exerted a chemotactic influence on the epithelial cells.

[1] Fischer: *Münch. Med. Wochenschrift*, Oct. 16, 1906.

His work has been repeated in this laboratory as nearly as was possible from the meagre description given of his technic. Three old and three young rabbits were injected under the skin of the ear with the Scharlach R-olive oil solution, and the injected tissue excised and examined at times varying from seven to sixty-one days. Our results show that the solution has absolutely no influence on the epithelial elements, but acts as a mild irritant, inducing a chronic inflammation with slight reaction on the part of the connective tissue in the case of the old rabbits, and a greater reaction with the formation of foreign body giant cells in the case of the young rabbits, the conclusion being that the attraxin theory is without sound foundation, in so far as "Scarlet-oil" is concerned.

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The effects of struggle on the content of white cells in the lymph.

By **F. PEYTON ROUS.** (Communicated by **ALDRED S. WARTHIN.**)

[*From the Pathological Laboratory, University of Michigan.*]

As the first stage of an investigation into the content of white cells in the lymph under certain common physiological and pathological conditions, the author has studied the effects on this content of variations in muscular activity. The lymph running from the thoracic duct was collected in a special mixing-tube — 3 c.c. of lymph to 3 c.c. of a 4 per cent. solution of sodium citrate in 0.8 per cent. salt solution — tinting accomplished with a trace of methyl violet, and counts made in the blood-counting chamber. Adult dogs under morphin and chloroform were used.

Preliminary determinations, with the animal quiet, showed that for any one individual the number of leukocytes per c.mm. of lymph was practically a constant during the 1–4 hours in which observations were made. Thus certain unavoidable changes in the body state — increased concentration of the blood as the body lymph drained away, variations in the amount of anesthetic — could for later work be ruled out as regards any marked influence in lymph's cell content.

The effects of struggle were then taken up. With struggle, as others have shown, the lymph flow increases sharply in amount for a few minutes. With this the author found a corresponding increase in cell content, an increase marked in "cell concentration" per c.mm. of lymph and in the total number of elements passed. Specimens taken at short intervals showed that the curve of increase in cell concentration was not coincident with that of the lymph flow, but was somewhat retarded, the greatest cell increase often existing in the few c.c. of lymph obtained in the quiet immediately following muscular exertion. That a transient flushing out of cells was not responsible for the main results, was shown by the data from long-continued struggle. The cell content and concentration remained high throughout, even when the rate of lymph flow had lessened to that seen previously during quiet. In an instance in which struggle was prolonged to 35 min. slightly more than twice as much lymph was voided, and over four times as many cells, as in the 35 min. of quiet immediately preceding. Following such prolonged exertion the lymph was for a time poorer in cells than previous to it.

An additional conclusion reached was that, for a given individual, the lymph glands seem "set" to produce cells at definite rate. This rate has a wide range for reasons unknown. The cell increase with struggle comes from the peripheral lymph system rather than from sedimented cells in the receptaculum chyli, and is probably dependent on another factor besides increased lymph flow (a supposition upheld by later experiments with lymphagogues). The facts elicited have a bearing on the "physiological mononucleosis" of the blood observed in man following active exercise, on the disappearance of this following prolonged exertion (25 mile run), and the absolute decrease in mononuclears sometimes seen.

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A lipolytic form of hemolysis.

By HIDEYO NOGUCHI.

[*From the Rockefeller Institute for Medical Research.*]

The varieties of hemolysis hitherto described imply the direct action of certain chemically-defined bodies, acids, alkalis, glucosides,

— which attack and destroy the integrity of the red corpuscles, and other chemically undefined bodies, — bacterial hemolysins, which act in the same manner, and the more indirect action of certain complexes defined as intermediary body and complement. I have shown previously that certain soaps and fatty acids — of the oleic series, chiefly — can play the part of complements in hemolysis. The experiments based upon this fact led me to the study of the ferment lipase as the direct or indirect cause of hemolysis. I found in the course of this study that lipase is, under some conditions, an efficient hemolytic agent which acts, however, not directly upon the red corpuscles, but indirectly through the liberation from available fats of the active fatty acids. Neutral fats, the higher glycerides, are not hemolytic, but they become so under the influence of lipase.

If one drop of triolein, or a corresponding amount of fat from the dog or guinea-pig, or a small quantity of tripalmitin or crotin, is added to 2 c.c. of a 5 per cent. suspension of washed red corpuscles and 1 c.c. of the lipase solution be added, hemolysis will occur. Neither the lipase nor the fats alone are lytic. Lecithin cannot replace the fats mentioned. The hemolysis is non-specific. Serum of the dog and the guinea-pig, and, to a less extent, of the ox are rendered non-specifically hemolytic by the action of lipase.

Potassium cyanide and sodium fluoride in 1 : 10,000 solution inhibit the action of lipase on the fats, and calcium chloride removes the lytic agent from an active mixture. Since the bile salts are known to increase lipolysis, the effects of the sodium salts of cholic, glycocholic and taurocholic acids in 1/500 *N* solutions were tested on lipolytic hemolysis. The rate of hemolysis was accelerated.

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On the mechanism by which water is eliminated from the blood capillaries in the active salivary glands.

By **A. J. CARLSON, J. R. GREER** and **F. C. BECHT.**

[*From the Hull Physiological Laboratory of the University of Chicago.*]

1. There is a spontaneous flow of lymph from the quiescent parotid gland of the horse. The quantity is never great but it was

evident in all of our nine experiments. It is probable that part of the lymph that flows from the neck lymphatics in an anesthetized dog with all the salivary glands at rest comes from the salivary glands. This fact necessitates a limitation of Asher's theory of lymph production.

2. When the parotid of the horse is thrown into activity by stimulation of the cranial secretory nerves or by injection of pilocarpin into the blood there is no appreciable increase in the output of lymph from the gland as compared with that from the gland at rest. This is true both of the spontaneous flow and of the flow aided by direct massage of the gland.

3. The activity of the submaxillary does not appreciably influence the flow of lymph from the neck lymphatic in the dog. This conclusion is based on experiments on thirteen dogs. If the activity of the submaxillary gland increases the output of lymph from the neck ducts, the increase is too slight to be detected by our present method, and is not one-tenth of the saliva eliminated by the gland, as Barcroft's observations would seem to demand. Our experiments were made on the spontaneous flow; on the flow aided by movements of the lower jaw by a mechanical contrivance to secure absolute uniformity in rate and amplitude; and on the flow aided by direct massage of the head and neck by kneading. Moreover a check was introduced by way of recording the lymph flow from both neck ducts, while the submaxillary gland on one side only was thrown into periodic activity by chorda stimulation. As our results are directly contrary to those of Asher and Bainbridge, the question should be reinvestigated by others.

4. In dogs under light ether anesthesia, perfectly quiescent and with all the salivary glands at rest, there is always a spontaneous flow of lymph from the neck lymphatics. If the anesthesia is pushed till the blood pressure falls considerably, this spontaneous flow ceases. The fact that Asher and Bainbridge worked on dogs under morphin may account for their failure to obtain lymph from the neck ducts in the absence of massage.

5. The osmotic pressure of the lymph from the active parotid of the horse is not the same in all animals. It may be either the same, higher or lower than that of the serum. In fact in three out of our five experiments it was lower. In four of the experi-

ments we failed to secure sufficient quantities of lymph from the gland for the freezing point determination. Since we have only five experiments on which to base our deductions, we do not consider the above statements final; but the fact that the lymph obtained from the active gland had in three cases considerably lower osmotic pressure than the serum, apparently eliminates osmosis as the factor effecting the transfer of water from the blood capillaries in the active gland. That leaves the secretory nerve theory and the "hormone" theory, as before stated, the only occupants of the field. The latter seems to us the most probable one, and our work is now directed towards proving or disproving it.

6. The osmotic pressure of the lymph from the neck lymphatics of the horse, collected with the animal under chloroform anesthesia, may be of slightly higher, of the same or of considerably lower osmotic pressure than the serum. Hamburger states that the osmotic pressure of the lymph collected from the neck lymphatic of the horse is thirteen per cent. higher than that of the serum. Hamburger collected the lymph from animals not under anesthesia.

We ourselves have had two cases which showed that the osmotic pressure of the neck lymph was more than one atmosphere lower than that of the serum. Here we are face to face with the old problem of secretion of urine, only here the relation is reversed. Even assuming that the capillary pressure in the head and neck region of the horse is 100 mm. Hg., this would not avail to overcome the difference in osmotic pressure of the lymph and the serum in these two cases, so that filtration could be the factor in the lymph production. Unless the lymph in these two cases was rendered dilute by the absorption by the tissue cells of the constituents making up the osmotic pressure, which although improbable is now being investigated, we have here a demonstration of a formation of lymph by a secretory activity of the capillary walls.

7. The osmotic pressure of the lymph from the neck lymphatics of the dog is usually lower than that of the serum. It is rarely greater. Leathes states that the thoracic lymph of the dog is always of higher osmotic pressure than the serum. In two of our experiments we collected lymph also from the thoracic duct, finding it in both cases of higher osmotic pressure than the neck

lymph. The thoracic lymph was in one case of the same, in the other case, of a higher osmotic pressure than the serum. It is therefore probable that the osmotic pressure of the thoracic lymph is usually greater than that of the neck lymph.

8. Under the conditions of our experiments — ether or chloroform anesthesia for from two to four hours — the osmotic pressure of the serum at the end of the experiment was in many cases greater than at the beginning of the experiment. The same difference is sometimes exhibited by the lymph collected from the same lymphatic but at different periods of the experiment. The mechanism of this change is being investigated.

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On the dissociation in solutions of the neutral caseinates of sodium and ammonium.

By T. BRAILSFORD ROBERTSON.

[*From the Rudolph Spreckels Physiological Laboratory of the University of California.*]

From the dilution law, or from the equations for the equilibrium of an amphoteric electrolyte in the presence of non-amphoteric electrolytes, it can be shown that in the case of a protein in which the acid function considerably exceeds the basic function (as, for example, in the case of casein), an equation can be obtained connecting the observed conductivity of a neutral solution of the protein compound of a base with the dilution of the solution. This equation involves two constants, the one being the dissociation-constant of the protein salt of the base and the other the sum of the specific velocities of the anions and cations present.

If a solution of a hydroxide of an alkali or alkaline earth or ammonia be shaken up with casein until no more casein goes into solution, the solution (as I have previously shown) is, after filtration, neutral in reaction and is a solution of the neutral caseinate of the base, containing an amount of the base equivalent to 2.4 per cent. CaO.

Since these solutions are neutral, if no complex ions are formed, the conductivity will be entirely due to the cations of the base employed and to the casein anions. The sum of the ionic

velocities obtained from the above-mentioned equation will therefore be greater than the specific velocity of the cation of the base by the specific velocity of the casein anion. In the case of the neutral caseinate of sodium the sum of the ionic velocities was found to be slightly greater than the velocity of the Na ion, indicating a specific velocity of 2.6×10^{-5} cm. per sec. for the casein anion at 25°. In the case of ammonium caseinate, however, the sum of the ionic velocities was found to be considerably *less* than the specific velocity of the ammonium ion. This can only be interpreted, I think, as indicating the presence in this solution of complex cations containing ammonium. Other considerations show that the effect is not due to viscosity. If casein be regarded as an ampholyte of the type HXOH, the sodium salt would be of the type $Na^+ + XOH^-$; it is possible that the ammonium salt in solution forms ions of the type $NH_4X^+ + OH^-$ or $NH_4X^+ + XOH^-$.

So far as I am aware, this constitutes the first direct experimental indication of the actual existence, in vitro, of the compounds of protein and alkalies and alkaline earths in which the non-protein ion is not dissociable as such, the existence of which, in living tissues, has been pointed out by Loeb.

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The Altmann's granules in kidney and liver and their relation to granular and fatty degeneration.

By **WILLIAM OPHÜLS.**

[*From the Pathologic Laboratory of Cooper Medical College, San Francisco, Cal.*]

In the kidneys of dogs, rabbits and guinea pigs we find the following arrangement of the Altmann's granules: In the connecting, the convoluted tubules and in the descending parts of the loops of Henle, the granules are rather coarse, very definitely rodshaped and arranged in radial rows in the basilar two thirds of the cells, often so closely set end to end that it is difficult to make out the dividing lines between them. In the part of the cells directly adjoining the lumen there are few scattered short

rodshaped granules and none in the "Bürstenbesatz." These details are naturally more plainly shown in the large cells of the convoluted tubules but in a general way the smaller cells in the connecting tubules and in the descending loops of Henle resemble them very closely. Some groups of convoluted tubules have much coarser granules than others. I have not been able to make out whether this is a constant anatomic difference or due to different functional stages. If the granules have any relation to the function of the cells, which seems probable, one would surmise that the connecting tubules cannot purely serve the function of conducting the urine from one place to another, all the more so as in the large ducts in the pyramids which serve this purpose alone, the granules are very scanty and irregularly arranged. In the large light cells of the ascending parts of the Henle's loops the granules are exceedingly small, also slightly rodshaped, extremely numerous and scattered all through the cells in an irregular fashion. This might be used as an argument in favor of a difference in function of this portion of the tubules. In the cells of the liver of these animals the granules vary greatly in size from just visible to quite coarse granules. All of them are rods, some short, others quite long and more or less wavy. The granules are scattered irregularly all over the cells.

In granular degeneration the characteristic macroscopic and microscopic pictures of which can be best produced by intravenous injection of bichromate of potash, the granules enlarge in size, become more or less spherical, lose their normal arrangement and stain very deeply with Altmann's stain contrary to what has been generally assumed after the work of Schilling,[1] who seems to be the only one to have investigated this question. Whether there is an actual multiplication of the granules, it is difficult to decide but on the whole the evidence seems against it. The change is almost exclusively in the convoluted tubules; the connecting tubules and the loops of Henle as a whole are slightly affected if at all. In the liver the change is similar, all cells being equally involved. The albuminous granules in granular degeneration, then, are not new formed granules but largely the enlarged and disarranged normal Altmann granules. I was able to confirm this

[1] Schilling: *Virch. Arch.*, 1897, cxxxv, p. 410.

view in two pronounced cases of parenchymatous degeneration in man.

The relation of the Altmann's granules to fat absorption and fat secretion has already been studied carefully by Altmann himself and his pupils Krehl and Metzner, and they have also touched upon the behavior of the granules in fatty degeneration in phosphorus poisoning. Their conclusion is that fat in all cases appears first in and around the Altmann's granules ; they even succeeded in demonstrating remnants of the granules in the center of the initial fat droplets. My observations on the kidneys and liver are confirmatory of these views, although I never succeeded in seeing these remnants of granules in the center of the first fat droplets. It seemed more as if the granules were changed to fat in toto. In fatty degeneration (I use this term for want of a better one) the granules first stain gray with osmic acid and do not take the acid fuchsin stain any more. They may still retain their rod shape. Later they become black and round. The first fat droplets invariably have very nearly the size and in a general way the arrangement of the Altmann's granules. Larger droplets are formed by the fusion of these small ones. I am far, however, from concluding with Altmann that these changes indicate any vital activity in the granules. I should rather imagine that a considerable part of their substance normally must be made up of a combination of fats which does not give the usual reaction of fat and that during fatty degeneration this combination is broken up and the fat liberated.

These observations furnish some explanation why granular and fatty degeneration so frequently occur simultaneously, both being the result of abnormal conditions in the Altmann's granules.

I am greatly indebted to the Rockefeller Institute for financial aid in carrying out these experiments.

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The relation of anatomic structure to function.

By **WILLIAM OPHÜLS.**

[*From the Pathologic Laboratory of Cooper Medical College, San Francisco, Cal.*]

It is a well known fact that function is often disturbed without corresponding anatomic lesion. There is always a suspicion, however, that the lack of demonstrable lesion is only apparent and really to be attributed to our crude methods of investigation and our lack of knowledge of the physiologic arrangements. As the Altmann method reveals some very fine details of the protoplasm, and as Altmann has shown that during normal function, especially when stimulated by injections of pilocarpin, the appearance and arrangement of the granules, brought out by his method in the protoplasm, changes quite remarkably, they being in many cases extruded to form part of the secretion, I thought it interesting to see whether these structures would serve as indicators of any primary alteration in the protoplasm of cells during functional disturbances.

The kidney appeared to be the organ best suited for this purpose as by collection of the urine directly after its discharge from the ureters, the exact moment of the occurrence of the disturbance could be ascertained. It is possible to produce albuminuria in dogs within a few hours by intravenous injection of bichromate of potash (about 2–3 c.c. of a 2% solution). If Altmann's specimens are made from the kidneys at this time no lesions are found. That the poison nevertheless acts upon the epithelial cells and the granules in them is shown by the subsequent development of severe lesion in them.

In phloridzin glycosuria, likewise, no lesions are demonstrable by this method, although we are fairly certain that the excretion of sugar in this case is due to a lesion in the kidney.

I am inclined to believe that quite a few of the anatomic changes which we now look upon as primary are the result rather than the cause of the functional disturbance, although the disarrangement brought about by them naturally often aggravates the

original condition. It is questionable whether the real primary lesion in such cases is of such character as to be ever demonstrable by physical methods.

I am greatly indebted to the Rockefeller Institute for financial aid in carrying out these experiments.

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Proteid poisons.

By VICTOR C. VAUGHAN.

[*From the Hygienic Laboratory, University of Michigan.*]

We have been able by diverse methods to split proteids, bacterial, vegetable and animal, into poisonous and non-poisonous products. The purpose of this abstract is to state briefly some of the properties of the poisons obtained by the cleavage of proteids.

The poisons obtained from the different proteids are similar but are not identical. All are soluble in both water and absolute alcohol, more freely in the latter than in the former. The aqueous solutions are acid and slowly decompose sodium bicarbonate, forming salts apparently, and these are less poisonous than the free acids. The aqueous solutions give the general color reactions for proteids with the exception of that of Molisch, and some of them give this reaction. However, most of the proteid poisons obtained by cleavage of the proteid molecule contain no carbohydrate and are free from phosphorus.

These poisons when injected into animals intra-abdominally, subcutaneously or intravenously induce characteristic symptoms and when administered in sufficient quantity kill promptly. There is a first stage which may be designated as that of peripheral irritation, which is characterized by restlessness and scratching. In the second stage there is partial paralysis, most marked in the posterior extremities; the third stage is characterized by more or less violent clonic convulsions and in the great majority of instances these terminate in death within half an hour after administration. Animals may show the first and second stages and still recover, but in the great majority the appearance of the convulsive stage indicates a fatal termination. As a rule death or recovery results within one hour and the former may occur within five minutes and,

with an intravenous injection, the time may be even shorter than this. The fatal dose may vary from eight to one hundred milligrams according to the purity of the poison or the mode of administration. While the fatal dose may be small the range between that necessary to induce the first and second stages and that necessary to kill may be wide. With one preparation seventy milligrams was required to kill, but five milligrams developed the first and second stages in pronounced forms.

Death is due to failure of respiration and the heart often continues to beat for some minutes after respiration has ceased. It seems most probable that death is due to the direct action of the poisons on the respiratory center. It is inferred from the readiness with which recovery may follow non-fatal doses that the poison cripples but does not destroy the cells of the respiratory center.

All attempts to produce antitoxins with these proteid poisons have, so far, failed. It is true that repeated treatments of animals with non-fatal doses of the poisons from the colon and typhoid bacilli enable animals to bear from two to four times the ordinarily fatal doses of living cultures of these bacteria, but this seems to be due to an increased resistance rather than to a true immunity. This condition is not specific and may be induced by the poisons obtained from peptone or egg white, as well as with that obtained by cleavage of the homologous bacterium.

Attempts have been made to ascertain the chemical constitution of the proteid poisons by splitting them up with mineral acids but at present these experiments have not yielded satisfactory knowledge and work along this line is being continued. The physiologic action of the proteid poisons leads to the suspicion that they contain a neurin group, but so far we have not been able to demonstrate the presence of such a body.

98 (241)

Observations on the living developing nerve fiber.

By **ROSS G. HARRISON.**

[*From the Anatomical Laboratory of the Johns Hopkins University.*]

The immediate object of the following experiments was to obtain a method by which the end of a growing nerve could be

brought under direct observation while alive, in order that a correct conception might be had regarding what takes place as the fiber extends during embryonic development from the nerve center out to the periphery.

The method employed was to isolate pieces of embryonic tissue known to give rise to nerve fibers, as for example, the whole or fragments of the medullary tube, or ectoderm from the branchial region, and to observe their further development. The pieces were taken from frog embryos about 3 mm. long, at which stage, *i. e.*, shortly after the closure of the medullary folds, there is no visible differentiation of the nerve elements. After carefully dissecting it out the piece of tissue is removed by a fine pipette to a cover slip upon which is a drop of lymph freshly drawn from one of the lymph sacs of an adult frog. The lymph clots very quickly, holding the tissue in a fixed position. The cover slip is then inverted over a hollow slide and the rim sealed with paraffine. When reasonable aseptic precautions are taken, tissues will live under these conditions for a week and in some cases specimens have been kept alive for nearly four weeks. Such specimens may be readily observed from day to day under highly magnifying powers.

While the cell aggregates, which make up the different organs and organ complexes of the embryo, do not undergo normal transformation in form, owing no doubt in part to the abnormal conditions of mechanical tension to which they are subjected, nevertheless the individual tissue elements do differentiate characteristically. Groups of epidermis cells round themselves off into little spheres or stretch out into long bands, their cilia remain active for a week or more and a typical cuticular border develops. Masses of cells taken from the myotomes differentiate into muscle fibers showing fibrillæ with typical striations. When portions of myotomes are left attached to a piece of the medullary cord the muscle fibers which develop will, after two or three days, exhibit frequent contractions. In pieces of nervous tissue numerous fibers are formed, though owing to the fact that they are developed largely within the mass of transplanted tissue itself, their mode of development cannot always be followed. However, in a large number of cases fibers were observed which left the mass of nerve tissue and ex-

tended out into the surrounding lymph clot. It is these structures which concern us at the present time.

In the majority of cases the fibers were not observed until they had almost completed their development, having been found usually two, occasionally three and once or twice four days after isolation of the tissue. They consist of an almost hyaline protoplasm, entirely devoid of the yolk granules, with which the cell-bodies are gorged. Within this protoplasm there is no definiteness of structure; though a faint fibrillation may sometimes be observed and faintly defined granules are discernible. The fibers are about 1.5–3 μ thick and their contours show here and there irregular varicosities. The most remarkable feature of the fiber is its enlarged end, from which extend numerous fine simple or branched filaments. The end swelling bears a resemblance to certain rhizopods and close observation reveals a continual change in form, especially as regards the origin and branching of the filaments. In fact the changes are so rapid that it is difficult to draw the details accurately. It is clear we have before us a mass of protoplasm undergoing amœboid movements. If we examine sections of young normal embryos shortly after the first nerves have developed, we find exactly similar structures at the end of the developing nerve fibers. This is especially so in the case of the fibers which are connected with the giant cells described by Rohon and Beard.

Still more instructive are the cases in which the fiber is brought under observation before it has completed its growth. Then it is found that the end is very active and that its movement results in the drawing out and lengthening of the fiber to which it is attached. One fiber was observed to lengthen almost 20 μ in 25 minutes, another over 25 μ in 50 minutes. The longest fibers observed were 0.2 mm. in length.

When the placodal thickenings of the branchial region are isolated, similar fibres are formed and in several of these cases they have been seen to arise from individual cells. On the other hand, other tissues of the embryo such as myotomes, yolk endoderm, notochord and indifferent ectoderm from the abdominal region do not give rise to structures of this kind. There can therefore be no doubt that we are dealing with a specific characteristic of nervous tissue.

It has not yet been found possible to make permanent specimens which show the isolated nerve fibers completely intact. The structures are so delicate that the mere immersion in the preserving fluid is sufficient to cause violent tearing and this very frequently results in the tearing away of the tissue in its entirety from the clot. Nevertheless, sections have been cut of some of the specimens and nerves have been traced from the walls of the medullary tube, but they were in all cases broken off short.

In view of this difficulty an effort, which resulted successfully, was made to obtain permanent specimens in a somewhat different way. A piece of medullary cord about four or five segments long was excised from an embryo and this was replaced by a cylindrical clot of proper length and caliber, which was obtained by allowing blood or lymph of an adult frog to clot in a capillary tube. No difficulty was experienced in healing the clot into the embryo in proper position. After two, three or four days the specimens were preserved and examined in serial sections. It was found that the funicular fibers from the brain and anterior part of the cord, consisting of naked axones without sheath cells, had grown for a considerable distance into the clot.

These observations show beyond question that the nerve fiber develops by the outflowing of protoplasm from the central cells. This protoplasm retains its amœboid activity at its distal end, the result being that it is drawn out into a long thread which becomes the axis cylinder. No other cells or living structures take part in this process. The development of the nerve fiber is thus brought about by means of one of the very primitive properties of living protoplasm, amboeoid movement, which, though probably common to some extent to all the cells of the embryo, is especially accentuated in the nerve cells at this period of development.

The possibility becomes apparent of applying the above method to the study of the influences which act upon a growing nerve. While at present it seems certain that the mere outgrowth of the fibers is largely independent of external stimuli, it is of course probable that in the body of the embryo there are many influences which guide the moving end and bring about contact with the proper end structure. The method here employed may be of value in analyzing these factors.

99 (242)

The presence of allantoin in the urine of the dog during starvation.

By **FRANK P. UNDERHILL.**

[*From the Sheffield Laboratory of Physiological Chemistry, Yale University.*]

The presence of allantoin in the urine, especially of carnivora, has afforded the impetus for a large number of investigations. A great deal of the interest manifested in this substance has been excited by its close chemical relationship to uric acid and the possible significance it may bear to uric acid metabolism. The consensus of opinion seems to indicate that the appearance of allantoin in the urine of the dog at least depends in large measure upon the type of proteid ingested. Thus, after feeding tissues or organs rich in nucleoproteid, or nucleoproteid itself, the quantity of allantoin eliminated is greatly increased. It is to the nuclein-containing radical of the proteid that the origin of allantoin has been ascribed. Other observations have shown that allantoin may appear in the urine under various pathological conditions involving destruction of nuclear material.

During the progress of an investigation upon intermediary metabolism it became necessary to subject the experimental animals to periods of starvation lasting from ten days to two weeks. From the urine of these dogs allantoin separated spontaneously in pure white crystals and the presence of this substance in the urine was constant. So far as I am aware, the presence of allantoin in the urine during starvation has not been recorded hitherto. This observation makes it probable that allantoin is a constant constituent of the urine of the dog.

100 (243)

Alkaloidal compounds of mucoids, nucleoproteins and other proteins.

By WALTER H. EDDY and WILLIAM J. GIES.

[*From the Laboratory of Biological Chemistry of Columbia University, at the College of Physicians and Surgeons.*]

In continuation of our studies of protein compounds we have observed that nucleoprotein, mucoid, caseinogen and alkali albuminate form water-soluble products with alkaloids. By intimately mixing samples of the purified moist protein and the pure alkaloid, especially with the latter in considerable excess, soluble products are formed, which may be precipitated by alcohol or alcohol-ether, and which, after purification and drying, readily dissolve in water. Such aqueous solutions are neutral to litmus, and the proteins may be readily precipitated from the solutions by slightly acidifying them.

Many such protein-alkaloid products have been made. The purest thus far obtained was prepared from mucoid and strychnin by the following general process: After thoroughly mixing moist mucoid with an excess of strychnin, the viscid mass was extracted several times with water and the centrifuged extracts were filtered and combined. The filtrates were faintly opalescent and neutral to litmus. They were evaporated nearly to dryness at 40° C. in shallow dishes in the presence of toluol, which was frequently renewed in small amounts. The protein-alkaloid product was precipitated from the concentrated solution by alcohol-ether added in large excess. The resultant precipitate was dissolved in water and the solution subjected to the previous evaporation process. The abundant dry residue thus obtained was finely pulverized and repeatedly extracted with large proportions of chloroform until no more strychnin could be removed, even after exposure to fresh chloroform for several days.

The resultant product possessed a very bitter taste, gave the common color reactions for protein, responded sharply to the oxidation test (with sulfuric acid and dichromate) for strychnin and dissolved readily in water, forming a clear solution. The aqueous

solution, which was neutral in reaction, yielded on acidification a bulky flocculent precipitate of mucoid; on rendering it alkaline, however, crystalline strychnin was immediately deposited in relative abundance.

Our observations suggest thus far that this preparation was a definite strychnin-mucoid salt, although we have not yet excluded the possibility that it was an adsorption product. Preliminary experiments indicate that it required from about three to four times as much of this product as of strychnin sulfate to produce tetanus promptly in dogs and frogs.

The purification of such products, and their chemical and pharmacological study, is under way.

Twenty fourth meeting.

Carnegie Institution's Station for Experimental Evolution, Cold Spring Harbor, Long Island, New York. June 22, 1907. President Flexner in the chair.

101 (244)

Demonstrations of methods and results of pedigree breeding of plants and animals.

By **CHARLES B. DAVENPORT.**

[*From the Carnegie Institution's Station for Experimental Evolution, Cold Spring Harbor, Long Island, N. Y.*]

Four series of pedigreed poultry were shown to illustrate certain laws of inheritance.

Series I. Darwin's case of "reversion":

1, Jungle fowl; 2, black minorca and 3, white silky, female; 4, their son, black with red markings as in the jungle fowl; 5, second hybrid generation, including (*a*), white type and (*b*), type with jungle fowl coloration.

Series II. The production of a frizzle-silky race:

1, Silky, male; 2, frizzle, female; 3, first hybrid generation, frizzled but not silky; 4, second hybrid generation, both frizzled and silky feathers in the same individual.

Series III. Particulate inheritance of plumage color:

1, Game colored Tosa fowl, male; 2, white cochin, female; 3, son of 1 and 2, game colored, feathers barred with white; 4, second hybrid generation: (*a*), white type; (*b*), game type.

Series IV. Independence in inheritance of the different characters:

1, White leghorn, male; 2, Houdan, female (mottled, black and white); 3, son of 1 and 2, white, small crest, Y comb, low nostril, four toes on each foot; 4, second hybrid generation, white, high nostril, no crest, heavy muff, four toes.

Demonstration of inheritance of characters in canaries.

Series I. Pure crest, crossed with crestless. Offspring all

crested. Second hybrid generation includes both crested and crestless birds.

Series II. Inheritance of plumage color: Green canaries crossed with yellow canaries give mottled offspring. Descendants of these mottled offspring include some yellow and also some green birds.

Demonstration of Œnothera (evening primrose) and its mutants.

Demonstration of branching and branchless sunflowers.

Demonstration by Miss Lutz of variability of chromosomes in Œnothera and its mutants.

Demonstration by Mr. F. E. Lutz of inheritance of abnormal wing venation in the vinegar fly, Drosophila.

102 (245)

Further studies of the effects of the exposure of sperm to X rays.

By **CHARLES R. BARDEEN.**

[*From the Anatomical Laboratory, University of Wisconsin.*]

Eggs of *Rana pipiens* fertilized by sperm exposed to Roentgen rays for one hour all develop abnormally. The abnormalities begin to appear during the gastrulation period. Cases of spina bifida are not uncommon. Out of a lot of several hundred eggs, nearly all of which were fertilized, only one specimen survived two weeks. This was much stunted in growth and very abnormal in shape. Out of 80 eggs of the common toad exposed only 15 minutes to the Roentgen rays but 4 larvæ have survived one month. Most of the larvæ were markedly abnormal in shape. Of the survivors, two are large and apparently normal and two are undersized. Only one individual out of 150 eggs fertilized by sperm exposed 37 minutes to the rays has survived one month and this individual is but half the normal length and breadth. Out of 250 eggs fertilized by sperm exposed to the Roentgen rays for an hour and ten minutes, all exhibited marked abnormalities of development and the least abnormal larva and longest survivor died a week after the eggs were fertilized.

The susceptibility of sperm of anura to the X rays is in marked contrast to that of paramecia. Exposure of paramecia for 12

hours to rays of the same intensity caused no visible effects on form, rate of division or process of conjugation.

I have exposed the sperm of the toad to heat at 50° and 65° C. for from 15 to 20 minutes. This exposure destroys the fertilizing power of most of the spermatozoa but the few eggs fertilized by such sperm develop normally. Sperm exposed for from 15 to 20 minutes to the following solutions: $\frac{1}{40}$ per cent. formol, 12.5 per cent. ethyl alcohol, 1 per cent. NaCl, $\frac{1}{32}$ per cent. HCl and $\frac{1}{32}$ per cent. KOH, has the power of fertilizing toad eggs. Practically all of the resulting larvæ which have been preserved appear normal at the end of one month after fertilization of the eggs. Sperm exposed to stronger solutions of the same substances for 15 to 20 minutes seems to lose power of fertilizing. No abnormal larvæ have developed from the few eggs thus fertilized.

The short breeding season of the toads prevented as extended a series of experiments along these lines as had been planned.

103 (246)

On the absorption of toxins by the nerves.

By **CYRUS W. FIELD.**

[*From the Research Laboratory of the Department of Health, of New York City.*]

In an article published in the *Archiv für experimentelle Pathologie und Pharmakologie*, Vol. 49, Meyer and Ransom stated as a result of their experiments that tetanus toxin enters the central nervous system through the motor nerves, and moreover that it passes to the cord by way of the axis cylinder. Since that time Meyer (1905) has demonstrated that diphtheria toxin after injection into the experimental animal, could be demonstrated in the peripheral nerves. In a large number of experimental animals injected with both tetanus and diphtheria toxin, I have been able to show that the toxin could be demonstrated in the peripheral nerves leading from the inoculated area, and by the use of the right dose, and at a certain time, free toxin could be demonstrated in the cord, and yet the other tissues of the body including the blood, liver, spleen and kidneys showed no free toxin.

Not only is this true for diphtheria and tetanus but it is likewise true for the toxin produced from *B. Botulinus* and also for colloidal ferric hydrate. In the case of colloidal ferric hydrate, by removing the nerves and cord, and subjecting them to treatment with a solution of hydrogen sulphide, I was able to detect the presence of iron. By using small doses I was able to show the presence of these colloids in the nerves near the points of injection and in the spinal cord, but of none whatever in the other tissues, except at the points of inoculation.

Guillian has demonstrated practically the same phenomena by injecting a solution of ferric chloride into the sciatic nerves of dogs and rabbits, and later injecting into the general circulation potassium ferrocyanide. He found prussian blue only in the part of the nerve above the point of injection. He also injected india ink into the sciatic nerves of these animals, and in these cases he could find no limit of ascension, but the particles showed for only a short distance below the point of injection. He came to the conclusion that these substances travel by way of the lymphatics. As a result of this work I have drawn the conclusion that tetanus toxin does not travel by way of the axis cylinder, by any specific attraction of the nerve tissue for this toxin, but it passes up because the lymphatic flow of the nerve is passing constantly from the periphery to the center. It is for this reason that the toxin when injected subcutaneously or intramuscularly is taken up by the nerves and passes to the cord, and the first symptom to develop is the local tetanus, because these are the first cells that come in contact with the toxin.

It is a well known fact that in giving diphtheria or tetanus toxin intravenously a much greater dose is required to cause death than when either is injected subcutaneously or intramuscularly. The reasons for this are first, that the toxin injected into the blood may be combined with some of the blood elements and therefore rendered inactive; second, that by injection into the blood, the toxin is diluted to a very great extent, whereas when injected subcutaneously, a portion passes into the lymphatics of the nerves and is not mixed with the general body fluids, before it has reached the central nervous system.

Cernovodeanu and Henri have recently published the results

of a very interesting experiment which bears out this theory. By ligating all the muscles and blood vessels in the leg of a guinea pig and then injecting the guinea pig with over a hundred fatal doses of tetanus toxin below the ligatures, the pig did not develop tetanus, but they were able to demonstrate a slight amount of tetanus toxin in the sciatic nerve; in other words, all flow of lymph to the limb was prevented except that which entered through the skin, and therefore there was only a slight flow of lymph up to the nerve.

The conclusion is then that tetanus toxin does not travel up the nerve by reason of any specific attraction of the nervous tissues, but because the lymphatic flow in the nerve is from the periphery toward the center.

104 (247)

On the formation of a specific precipitin in rabbits after inoculation with colloidal platinum and colloidal silver.

By **CYRUS W. FIELD.**

[*From the Research Laboratory of the Department of Health, of New York City.*]

Some time ago in testing the precipitating effect of rabbit serum on various positive and negative colloids I found that such serum precipitated colloidal platinum and colloidal silver to a fair degree. Serum from one rabbit precipitated colloidal platinum completely at 1–100, slightly at 1–200 and not at all at 1–500. This serum precipitated colloidal silver completely at 1–10, partially at 1–100 and not at all at 1–250. After receiving three injections of colloidal platinum in three weeks this rabbit's serum then precipitated colloidal platinum completely at 1–1,000, slightly at 1–1,250 and not at all at 1–1,500. Whereas it precipitated colloidal silver completely at 1–100, slightly at 1–250 and not at all at 1–500.

Serum from another rabbit originally precipitated colloidal platinum completely at 1–50, partially at 1–100 and not at all at 1–250. The same figures held good for colloidal silver. After three injections of colloidal silver during three weeks, this rabbit's serum precipitated the colloidal silver completely at 1–500, partially at 1–1,000 and not at all at 1–1,250, whereas colloidal

platinum was completely precipitated at 1–200, partially at 1–500 and not at all at 1–1,000.

In other words the precipitating power of the serum of the first rabbit, after it received three injections of the colloidal platinum, had increased from 1–100 to 1–1,000 or ten times, whereas for the colloidal silver there was only a very slight increase. Serum from the second rabbit, which received colloidal silver, increased its precipitating power from 1–100 to 1–500, whereas for the colloidal platinum, from 1–100 to 1–250. In both these rabbits there was then an increase in the precipitating power of the serum after injection with these colloidal metals, and it would seem that they increased more for the metal injected than for the other.

Unfortunately both of these rabbits died before I was able to complete this work. Nevertheless I have thought it best to report to this society the results of this study, for they seem very interesting. Other animals are undergoing treatment with these and other colloids and I hope that I shall be able to report more fully at our next meeting.

105 (248)

Remote results of transplantations of blood vessels.

By **ALEXIS CARREL.**

[*From the Rockefeller Institute for Medical Research.*]

This communication deals first with the evolution of the anastomoses, and secondly with the modifications of the walls, of the transplanted vessels.

The results of the arterio-arterial, veno-venous and arterio-venous anastomoses remained excellent after many months. No stenoses or aneurisms have been observed on the arterial anastomoses six to seven months after the operation. No stenosis occurs after the venous anastomosis: a cat, in which an Eck fistula was made eighteen months ago by Guthrie and myself is still in good health. The same is the case for the arterio-venous anastomosis: the jugular vein and the carotid artery of a dog were anastomosed by Guthrie and myself twenty two months ago and now strong thrill and pulsations are easily detected by palpation of the jugular vein.

The modifications of the vascular walls are produced mainly by the changes of blood pressure. No great change occurs if the blood pressure of the transplanted vessel be not modified. Segments of carotid, aorta or vena cava of one animal, transplanted in the carotid, aorta or vena cava of another animal of the same size and species, do not undergo any important anatomical modification. If blood pressure be diminished, the wall of the transplanted vessel becomes thinner. Six months after the operation, it was found that the wall of the carotid transplanted in the external jugular vein was thinner than the normal one. If blood pressure be increased, hypertrophy of the wall ensues. A segment of external jugular vein interposed between the cut ends of the carotid artery was a little dilated and its wall was as thick as the arterial wall, eight months after the operation. In other cases, there was no dilation of the lumen of the vessels. As a rule when a vein is anastomosed uniterminally to an artery, its lumen is found to be dilated, six or seven months after the operation. Nevertheless, after one year the lumen may progressively diminish in size, as was seen in a dog operated upon twenty two months ago.

It may be concluded that transplanted blood vessels adapt themselves to the pressure by thinning or thickening their walls.

106 (249)

The dependence of gastric secretion upon the internal secretion of the salivary glands.

By **JOHN C. HEMMETER.** (Communicated by **S. J. MELTZER.**)

[*From the Physiological Laboratory of the University of Maryland.*]

The relations of the gastric secretion to the salivary glands are illustrated by the following clinical and experimental observations:

1. In four cases of Mikulicz's disease with normal conditions of the blood the stomach was found to secrete no gastric juice during the course of the disease. Mikulicz's disease consists in a benign chronic swelling of all the salivary and lacrimal glands.

2. In dogs with accessory stomachs (Pawlow) the removal of all the salivary glands abolishes permanently all gastric secretion.

3. The gastric secretion is not started in such dogs by feeding

them with food masticated and well insalivated by other normal dogs.

4. The abolished gastric secretion is temporarily resumed by peritoneal or intravenous injections of extracts made of salivary glands of normal dogs.

5. This temporary resumption takes place even if the stomach be completely isolated from the central nervous system.

These observations justify the conclusion that normal gastric secretion depends upon the internal secretion of the salivary glands.

107 (250)

The influence of diuresis upon the toxic dose of magnesium salts.

By **S. J. MELTZER.**

[*From the Rockefeller Institute for Medical Research.*]

In the communication on the effects of subcutaneous injections of magnesium salts, John Auer and I stated that a dose of magnesium sulphate slightly larger than 1.75 gram per kilo is surely fatal for the rabbit. Lucas and I showed later that in nephrectomized animals the toxicity of the salts is greatly increased. At the April meeting I conducted an experiment demonstrating that in nephrectomized animals magnesium sulphate can become toxic even when given by mouth. These lines of experimentation have shown that the toxicity of magnesium salts depends upon the normal activity of the kidneys. I wish now to report the results of a series of experiments in which the effect of an increased renal activity was studied.

Briefly stated the results were as follows: A dose of 2 grams of magnesium sulphate per kilo is absolutely fatal for the rabbit; the animal dies of respiratory paralysis in less than an hour. All the animals recovered from the effects of such a dose, however, if an intramuscular injection of diuretin was given soon after the subcutaneous injection of the magnesium salt. Diuretin is theobromin and acts as a diuretic. The deeply narcotized animals usually urinate about fifteen or twenty minutes after its injection; by that time, at least, the bladder can be felt to be full. The largest dose

that should be given is about 0.1 gram. In larger doses diuretin itself is liable to become toxic.

In cases in which the dose of the magnesium salts exceeded 2 grams per kilo the injection of diuretin alone could not save the animals. But if in addition to the diuretin an intravenous infusion of 0.9 per cent. solution of sodium chloride was instituted, animals were seen to recover even from doses of magnesium salts amounting to as much as 2.25 grams per kilo. When still larger doses of magnesium salts were given the animals usually died of respiratory paralysis in less than fifteen minutes and before any diuresis could have been effected. However, I have seen animals recover even from doses of 2.5 grams per kilo if, in addition to the diuretin injection and the venous transfusion, artificial respiration was early resorted to. For doses larger than 2.5 grams per kilo all three measures together usually proved of no avail; with this dose the early death of the animal is usually due greatly to paralysis of the heart.

108 (251)

The toxicity of magnesium nitrate when given by mouth.

By **S. J. MELTZER.**

[*From the Rockefeller Institute for Medical Research.*]

It is a daily experience that large doses of magnesium sulphate can be taken by mouth without any other than a purgative effect. I have given to rabbits, by mouth, 7 grams or more of magnesium sulphate (in molecular solution) per kilo, without any unfavorable effects. The same applies also to magnesium chloride and some other magnesium salts. I have, however, discovered that magnesium nitrate when given by mouth is capable of producing a toxic effect like that of magnesium salts when introduced subcutaneously.

When a dose of 6 grams per kilo in molecular solution is given by mouth to a rabbit, the animal soon becomes paralyzed and narcotized and dies in thirty or forty minutes of respiratory paralysis. Fifteen or twenty minutes after the administration, the appearance and behavior of the animal is exactly like that of one which received magnesium sulphate subcutaneously (2 grams per kilo). A dose between 4 and 5 grams per kilo causes in general

the same symptoms but in a gradual way; the animal dies after five or six hours. A dose of between 3 and 4 grams causes no serious effects, but for six or eight hours after its administration the animal remains in a soporous state; it sits in one place with eyes closed and head drooping; a loud noise wakes it up and it attempts to move about or to eat, but in a few minutes it falls asleep again.

This toxicity of the magnesium nitrate is apparently due to its greater absorption from the gastro-intestinal canal. It is certainly not due to its diminished elimination through the kidneys; on the contrary it acts in some degree as a diuretic, and, when given by subcutaneous injection, the animal withstands a somewhat greater proportionate dose of the nitrate than of the sulphate or chloride, probably because the nitrate increases somewhat the diuresis. As to the share which the anion, the nitrate end of the compound, may have in the toxic effect, I do not wish to make a positive statement; but I doubt whether it is of any importance. I studied the toxic effects of sodium nitrate administered by mouth and compared the manifestations with those seen after administration of magnesium nitrate; the contrast was sharp. Even with a dose of 12 grams of the sodium nitrate per kilo there is never such an anesthesia or paralysis as that caused by the magnesium salts; on the contrary the animal is all excitement and restlessness. Besides, the late death of the animal after administration of sodium nitrate is due to circulatory disturbances, whereas after poisoning with magnesium salts, the animal dies of respiratory paralysis.

109 (252)

On the promoting influence of heated tumor emulsions on tumor growth.

By **SIMON FLEXNER** and **J. W. JOBLING.**

[*From the Rockefeller Institute for Medical Research.*]

We have on several occasions presented to this Society some of the results of the study of a transplantable sarcoma of the rat, and we wish to-day to record an effect on the growth of the tumor which is produced by inoculation of the rats with an emulsion of the tumor cells, previously heated for half an hour to 56° C. This

emulsion was injected into the peritoneal cavity and the fragments of living tumor are introduced beneath the skin. The promoting effect on the growth of the tumor fragments to be described became evident in several sets of experiments in which the same emulsion (unheated), blood serum, bouillon, salt and Ringer solutions were injected in the same manner, with which substances this promoting effect was not obtained. If the inoculation of the fragment of the tumor is made twenty four hours after the injection of the unheated emulsion, no difference is noted between the control rats, the rats injected with the other substances, and those injected with heated emulsion. But if the fragments are inoculated ten or more days (up to thirty days) later, then the number of tumors which develop in the rats receiving the heated emulsion tends to exceed the controls and the other series mentioned; they grow with greater rapidity so as to reach double the size of the controls or even a still greater size, and show a far smaller percentage of recoveries (retrogressions). This promoting influence is present, as stated, on the tenth day after inoculation, and indications exist tending to show that it is less effective at the expiration of thirty days. On the other hand, indications also exist tending to show that if the injections of heated emulsion are repeated once or twice at ten-day intervals, the conditions of the animal favoring the growth and persistence of the tumors can be maintained and possibly even still further increased.

110 (253)

On the chemical inactivation and regeneration of complement.

By **HIDEYO NOGUCHI.**

[*From the Rockefeller Institute for Medical Research.*]

The complementary substances of an active serum were supposed to be extremely labile bodies, but their stability has never been tested chemically. In this study, the action of various acids, alkalies and salts upon complements has been examined. The list of chemicals used is as follows: ACIDS — hydrochloric, nitric, sulphuric, phosphoric, formic, acetic, propionic, lactic, butyric, oxybutyric, oxalic, tartaric, citric, fumaric, maleinic, citraconic, itaconic, glycerophosphoric, uric and nucleic; ALKALIES — am-

monium hydrate, sodium hydrate, magnesium hydrate, calcium hydrate and barium hydrate; SALTS — sodium carbonate; *magnesium* sulphate, phosphate, acetate and carbonate; *calcium* sulphate, nitrate, phosphate, acetate, oxalate and carbonate; *barium* sulphate, phosphate and carbonate. Urea was also included.

It was found that all acids and alkalies are able to inactivate complements when used in sufficient concentrations. With monobasic acids it takes about 1 c.c. of $n/40$ solution to inactivate 1 c.c. of active serum. About 1 c.c. of $n/50$ solution of the acid is, as a rule, neutralized by the inherent alkalinity of the serum.

With alkalies 0.3 c.c. (ammonium hydrate 0.8 c.c.) is sufficient for inactivation. The acids and alkalies are, when used without serum, hemolytic in the quantities stated. But when mixed with the serum they — serum and chemicals — lose their activity mutually.

Alkaline salts of strong acids are not anti-complementary unless a certain limit of concentration is exceeded. Sodium carbonate is anti-complementary in a relative, but not in an absolute sense. All other salts employed are strongly anti-complementary, the magnesium salts being the least inhibiting. Calcium and barium salts of strong acids are absolute anti-complements, while the carbonates of these elements may or may not be active upon complements.

Complements which are inactivated by acids can be reactivated by neutralizing the acids with alkalies, and *vice versa*. The action of various acids, alkalies and salts upon complements renders the complement-deviation phenomenon for forensic purposes less safe, because the materials are often impure in practical cases.

Various soluble salts of oleic acid are accelerators of the complementary action of serum.

111 (254)

A study of the influence of lecithin on growth.[1]

By **A. J. GOLDFARB** (by invitation).

[*From the Laboratories of Biological Chemistry (at the College of Physicians and Surgeons) and Zoology, of Columbia University.*]

A reexamination of the evidence upon which was based the stimulating properties attributed to lecithin included experiments on tadpoles and very young kittens. Danilewski believed that lecithin (one part in about 15,000 of water) caused in tadpoles an increase of 300 per cent. in weight, and about 200 per cent. in size, over the control animals.

My own experiments included three series of over 1,200 tadpoles. In each series the lecithin varied in strength from 1/150 per cent. to 2 per cent. (the toxic concentration). In one series (1) the tadpoles were not fed, in another (2) they were given minced worm, in the third (3) they were given a liberal supply of plant debris.

The tadpoles that were kept in lecithin solutions did not show any greater increment in weight or size than the controls of the same series. There was a marked difference, however, in both the size and weight of tadpoles of one series compared with the tadpoles in the corresponding solution of another series, due to the kind (and presumably the amount) of food given. Individuals of series 1 were smallest and weighed least; those of series 3 weighed from 3 to 6 times as much and were twice as broad as the tadpoles in the same strength of solution in series 2.

Young kittens (over 50 in number) were treated as follows:

Series 1. Lecithin was injected subcutaneously daily in doses of from 0.0006 to 0.004 gram. Control animals received subcutaneously equal volumes of physiological salt solution. The increase in weight was somewhat greater in the kittens that received the lecithin.

Series 2. Lecithin was injected subcutaneously in doses of from 0.01 to 0.32 gram daily. The kittens that received the

[1] I am greatly indebted to Professor Gies and Dr. W. N. Berg for the lecithin made by them for use in these experiments.

lecithin gained, in some cases, as much as 7 per cent. over the control animals.

Series 3. Lecithin was fed daily in amounts of from 0.01 to 0.32 gram. With very few exceptions, these kittens weighed from 2 per cent. to 12 per cent. more than the controls.

The best results were obtained in the feeding experiments, with doses of from 0.04 to 0.16 gram daily ; yet under these conditions the actual difference in weight between the kittens fed with lecithin and those not so fed was small, amounting on an average to about 7 per cent. Whether the same quantity of any other fatty or simple nutrient compound would result in an equal increment has not yet been determined, but will be investigated with other matters bearing upon the interpretation of the results recorded above.

112 (255)

Comparative data for the elementary composition and the heat of combustion of collagen and gelatin.

By **CHARLOTTE R. MANNING** and **WILLIAM J. GIES.**

[*From the Chemical Laboratory of Wesleyan University, Middletown, Conn., and from the Laboratory of Biological Chemistry, of Columbia University, at the College of Physicians and Surgeons.*]

Comparative elementary analyses, as well as determinations of the heat of combustion, of many samples of connective tissue collagen and gelatin, have indicated that there is a closer agreement between the mother substance and its derivative, on these two planes of comparison, than the prevalent idea of their chemical relationship would indicate. The following sample data show this quite clearly :

	C Per cent.	H Per cent.	N Per cent.	Heat of combustion calories.
Tendocollagen[1]	48.85	8.01	18.02	5,387
Tendogelatin	48.28	7.84	17.56	5,350

These data were obtained before the experiments by Emmett

[1] Each of these products was desiccated (before analysis) to constant weight by the Benedict-Manning process in vacuo. See the *American Journal of Physiology*, 1905, xiii, p. 309.

and Gies [1] were begun. The differences between the above figures for nitrogen and hydrogen contents harmonize with the observation by Emmett and Gies that nitrogen is eliminated as ammonia when collagen is converted into gelatin by treatment with hot water, and also strengthen their conclusion that gelatin is not a simple hydrate of collagen.

113 (256)

On the fate of elastose after its subcutaneous or intraperitoneal injection: a preliminary inquiry into the origin and nature of Bence Jones's protein.

By **REUBEN OTTENBERG** and **WILLIAM J. GIES.**

[*From the Laboratory of Biological Chemistry, of Columbia University, at the College of Physicians and Surgeons.*]

Bence Jones's protein and crude elastose not only have several proteose properties in common, but, unlike the ordinary proteoses, each is precipitated from its aqueous solution when the latter is gently warmed. Bence Jones's protein occurs in the urine of patients suffering from sarcoma of bone marrow or from osteomalacia.[2] Bone contains considerable elastin-like material. The senior author's study of ligament elastin and its digestion products [3] and his isolation and analysis of osseoalbumoid,[4] an elastin-like constituent of bone, led him to think that Bence Jones's protein might be a transformation product of osseoalbumoid, although there are a number of important objections to such a view. At all events, the possibility that Bence Jones's protein may be a derivative of osseoalbumoid, and the great desirability of making our knowledge of this elusive protein more definite, led us to begin a study of a preliminary phase of the work that will be necessary to determine the points at issue.

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[1] Emmett and Gies: *Proceedings of the American Society of Biological Chemists*, Washington, 1907; *Journal of Biological Chemistry*, 1907, iii, p. xxxiii. Also *Proceedings of the American Physiological Society*, Washington, 1907; *American Journal of Physiology*, 1907, xix, p. xi.

[2] When such urines are warmed, Bence Jones's protein, if present, is precipitated.

[3] Richards and Gies: *American Journal of Physiology*, 1902, vii, p. 93; also, Gies and collaborators: *Biochemical Researches*, 1903, i, Reprint No. 4.

[4] Hawk and Gies: *American Journal of Physiology*, 1902, vii, p. 340; also Gies and collaborators: *Biochemical Researches*, 1903, i, Reprint No. 6.

We sought first to ascertain whether crude elastose, when injected subcutaneously or intraperitoneally, is eliminated in the urine and whether it can be detected there by the heat-precipitation test. When thus introduced in dogs, crude elastose, obtained by peptolysis of ligament elastin prepared by Richards and Gies's method, not only promptly appears in the urine, but may be identified in it by the heat-precipitation test. This observation makes it clear that if elastose is formed in bone or in any other tissue by any pathological process, the elastose thus produced may pass into the urine without material alteration of the characteristic property referred to.

Before proceeding further in this connection, osseoalbumoid (bone elastin ?) will be prepared in sufficient quantity to permit of a determination of the nature of its proteoses and their fate when injected into animals.

RECAPITULATION OF THE NAMES OF THE AUTHORS AND OF THE TITLES OF THE COMMUNICATIONS.

VOLUME IV.

Abbott, F. M. [with **Warren P. Lombard.**]

146.[1] The inconstant action of muscles.

Auer, John

151. Gastric peristalsis under normal and certain experimental conditions.

152. [With **S. J. Meltzer.**] Reflex inhibition of the cardia in rabbits by stimulation of the central end of the vagus.

173. [With **S. J. Meltzer.**] Peristaltic movements of the rabbit's cecum and their inhibition, with demonstration.

Bardeen, Charles R.

245. Further studies of the effects of the exposure of sperm to X rays.

Beatty, W. A. [with **P. A. Levene.**]

219. On decomposition of uric acid by animal tissues.

221. On lysinglycyl obtained in the tryptic digestion of egg albumen.

Becht, F. C. [with **A. J. Carlson** and **J. R. Greer.**]

236. On the mechanism by which water is eliminated from the blood capillaries in the active salivary glands.

Beebe, S. P.

188. The parathyroid gland, with demonstrations of the effects of hypodermic injections of parathyroid nucleoproteid after parathyroidectomy.

226. [With **George W. Crile.**] Transfusion experiments in dogs showing artificially implanted tumors.

Berg, William N. [with **William J. Gies.**]

159. Further observations of the effects of ions on the activity of enzymes.

[1] The numerals correspond with those in parenthesis above the abstracts (pages 1–162).

Briggs, C. E. [with **J. J. R. Macleod.**]

168. On the supposed existence of efferent fibers from the diabetic center to the liver.

Burton-Opitz, Russell

163. The influence of the red corpuscles upon the viscosity of the blood.

164. A new recording stromuhr, with demonstration.

165. The influence of gelatin upon the viscosity of the blood.

182. On the competency of the venous valves and the venous flow in relation to changes in intra-abdominal pressure.

183. On vasomotor nerves in the pulmonary circuit.

202. The influence of adrenalin upon the venous blood flow.

203. The viscosity of laked blood.

213. On the influence of CO_2 on the viscosity of the blood.

Buxton, B. H.

145. Bile media in typhoid diagnosis.

Calkins, Gary N.

181. Spirochæta microgyrata (Löw) and mouse tumors.

Cannon, Walter B.

148. On the motor activities of the alimentary canal after splanchnic and vagus section.

Carlson, A. J. [with **J. R. Greer** and **F. C. Becht.**]

236. On the mechanism by which water is eliminated from the blood capillaries in the active salivary glands.

Carrel, Alexis

170. Heterotransplantation of blood vessels.

171. Transplantation of the kidney with implantation of the renal vessels in the aorta and vena cava.

206. Extirpation of both kidneys from a cat and transplantation of both kidneys from another cat, with exhibition of specimens.

227. Transplantation of the thigh from one dog to another.

248. Remote results of transplantations of blood vessels.

Collins, K. R. [with **Robert B. Gibson.**]

158. On the fractionation of agglutinins and antitoxin.

Conklin, Edwin G.

169. Experimental studies on nuclear and cell division.

Crampton, H. E.

187. A study of the vital conditions determining the distribution and evolution of snails in Tahiti, with illustrations.

Crile, George W.

149. Experimental and clinical observations upon direct transfusion of blood.

189. Further experimental and clinical observations on the transfusion of blood.

190. [With **D. H. Dolley.**] A preliminary report on the direct transfusion of blood in animals given excessive doses of diphtheria toxins.

191. [With **J. J. R. Macleod.**] The effect on the normal dog heart of expressed tissue juice from hearts of dogs poisoned with diphtheria toxin.

226. [With **S. P. Beebe.**] Transfusion experiments in dogs showing artificially implanted tumors.

Davenport, Charles B.

244. Demonstrations of methods and results of pedigreed breeding of plants and animals.

Dolley, D. H. [with **George W. Crile.**]

190. A preliminary report on the direct transfusion of blood in animals given excessive doses of diphtheria toxins.

Eddy, Walter H. [with **William J. Gies.**]

243. Alkaloidal compounds of mucoids, nucleoproteins and other proteins.

Emerson, Haven

179. The pathology of function: an experimental laboratory course.

212. Intra-abdominal pressures.

Ewing, James

223. Hemolysis in eclampsia.

Field, Cyrus W.

156. [With **Oscar Teague.**] The action of the electric current on toxin and antitoxin.

246. On the absorption of toxins by the nerves.

247. On the formation of a specific precipitin in rabbits after inoculation with colloidal platinum and colloidal silver.

Flexner, Simon

154. [With **J. W. Jobling.**] Remarks on and exhibition of specimens of a metastasising sarcoma of the rat.

167. The enzymotic properties of diplococcus intracellularis.

176. [With **J. W. Jobling.**] On secondary transplantation of a sarcoma of a rat.

229. Direct silver staining of spirochetes and flagellated bacteria.

252. [With **J. W. Jobling.**] On the promoting influence of heated tumor emulsions on tumor growth.

Folin, Otto

215. On the separate determination of acetone and diacetic acid in diabetic urines.

Foster, Nellis B. [with **A. V. S. Lambert.**]

155. The influence of water on gastric secretion and the chemical affinity of mucus for HCl in the stomach.

Gies, William J.

159. [With **William N. Berg.**] Further observations of the effects of ions on the activity of enzymes.

243. [With **Walter H. Eddy.**] Alkaloidal compounds of mucoids, nucleoproteins and other proteins.

255. [With **Charlotte R. Manning.**] Comparative data for the elementary composition and the heat of combustion of collagen and gelatin.

256. [With **Reuben Ottenberg.**] On the fate of elastose after its subcutaneous or intraperitoneal injection: a preliminary inquiry into the origin and nature of Bence Jones's protein.

Gibson, Robert B. [with **K. R. Collins.**]

158. On the fractionation of agglutinins and antitoxin.

Goldfarb, A. J. [by invitation.]

254. A study of the influence of lecithin on growth.

Greer, J. R. [with **A. J. Carlson** and **F. C. Becht.**]

236. On the mechanism by which water is eliminated from the blood capillaries in the active salivary glands.

Harrison, Ross G.

241. Observations on the living developing nerve fiber.

Hatcher, Robert A. [with **C. G. L. Wolf.**]

144. The formation of glycogen from sugars by muscle, with a demonstration of a perfusion apparatus.

Hawk, Philip B. [with **Thomas A. Rutherford.**]

196. Comparative chemical composition of the hair of different races.

Hemmeter, John C.

249. The dependence of gastric secretion upon the internal secretion of the salivary glands. [Communicated by **S. J. Meltzer.**]

Henderson, Lawrence J. [by invitation.]

201. Concerning the neutrality of protoplasm.

Herter, Christian A.

230. On the bacterial production of skatol and its occurrence in the human intestinal tract.

Hinkel, F. C. [with **William Salant.**]

180. The influence of alcohol on the composition of urine.

Jackson, Holmes C. [with **Richard M. Pearce.**]

192. Experimental liver necrosis: 1. Hexon bases.

Jobling, J. W. [with **Simon Flexner.**]

154. Remarks on and exhibition of specimens of a metastasising sarcoma of the rat.

176. On secondary transplantation of a sarcoma of the rat.

252. On the promoting influence of heated tumor emulsions on tumor growth.

Kast, Ludwig [with **S. J. Meltzer.**]

209. The abolition of visceral pain by intramuscular injection of cocaine.— A demonstration.

Lamb, Arthur B. [by invitation.]

225. An hydrodynamic explanation of mitotic figures.

Lambert, A. V. S. [with **N. B. Foster.**]

155. The influence of water on gastric secretion and the chemical affinity of mucus for HCl in the stomach.

Lee, Frederic S.

162. The cause of the treppe.

Levene, P. A.

157. [With **J. E. Sweet.**] Nuclein metabolism in a dog with an Eck fistula.

186. A method for separating leucin from amino-valerianic acid.

219. [With **W. A. Beatty.**] On decomposition of uric acid by animal tissues.

220. On the diuretic action of thymin.

221. [With **W. A. Beatty.**] On lysinglycyl obtained in the tryptic digestion of egg albumen.

Levin, Isaac

178. Effects of experimental injuries of the pancreas.

Lillie, Ralph S.

222. The osmotic pressure of colloidal solutions and the influence of electrolytes and non-electrolytes on such pressure.

Loeb, Jacques

195. On the nature of the process of fertilization.

Loeb, Leo

207. Wounds of the pregnant uterus.

208. The effect of light on the staining of cells.

Lombard, Warren P. [with **F. M. Abbott.**]

146. The inconstant action of muscles.

Lucas, D. R.

150. [By invitation.] On the normal peristaltic movements of the ureter.

153. [With **S. J. Meltzer.**] Continuous anesthesia by subcutaneous injection of magnesium sulphate in nephrectomized animals.

McGuigan, Hugh [with **A. P. Mathews.**]

197. The oxidation of sugars by cupric acetate-acetic acid mixtures.

Macallum, A. B.

193. The action of nitric acid on the phosphorus of nucleoproteids and paranucleoproteids.

Macleod, J. J. R.

168. [With **C. E. Briggs.**] On the supposed existence of efferent fibers from the diabetic center to the liver.

191. [With **George W. Crile.**] The effect on the normal dog heart of expressed tissue juice from hearts of dogs poisoned with diphtheria toxin.

MacNeal, Ward J.

231. A spirochete found in the blood of a wild rat.

Manning, Charlotte R. [with **William J. Gies.**]

255. Comparative data for the elementary composition and the heat of combustion of collagen and gelatin.

Marriott, W. McKim [with **C. G. L. Wolf.**]

204. The determination of ammonia and urea in blood.

Martin, A. A. (by invitation) [with **Allan C. Rankin.**]

198. Observations on the effects of fasting upon the opsonic power of the blood to staphylococcus aureus.

Mathews, A. P. [with **Hugh McGuigan.**]

197. The oxidation of sugars by cupric acetate-acetic acid mixtures.

Meltzer, S. J.

152. [With **John Auer.**] Reflex inhibition of the cardia in rabbits by stimulation of the central end of the vagus.

153. [With **D. R. Lucas.**] Continuous anesthesia by subcutaneous injection of magnesium sulphate in nephrectomized animals.

172. Secondary peristalsis of the esophagus — a demonstration on a dog with a permanent esophageal fistula.

173. [With **John Auer.**] Peristaltic movements of the rabbit's cecum and their inhibition, with demonstration.

174. Deglutition through an esophagus partly deprived of its muscularis, with demonstration.

209. [With **Ludwig Kast.**] The abolition of visceral pain by intramuscular injection of cocaine. — A demonstration.

210. The effect of nephrectomy upon the toxicity of magnesium sulphate when given by mouth. — A demonstration.

211. Observations on a rabbit for thirty months after the removal of the superior cervical ganglion.

249. [For **John C. Hemmeter.**] The dependence of gastric secretion upon the internal secretion of the salivary glands.

250. The influence of diuresis upon the toxic dose of magnesium salts.

251. The toxicity of magnesium nitrate when given by mouth.

Mendel, Lafayette B.

194. Does the stomach of the dog contain free hydrochloric acid during gastric digestion?

Murlin, J. R.

224. Glycocoll nitrogen in the metabolism of the dog.

Noguchi, Hideyo

177. On certain chemical complementary substances.

217. On the extracellular and intracellular venom activators, with special reference to lecithin, fatty acids and their compounds.

218. On the influence of the reaction, and of desiccation, upon opsonins.

235. A lipolytic form of hemolysis.

253. On the chemical inactivation and regeneration of complement.

Novy, Frederick G.

175. Immunity against trypanosomes.

Ophüls, William

238. The Altmann's granules in kidney and liver, and their relation to granular and fatty degeneration.

239. The relation of anatomic structure to function.

Opie, Eugene L.

205. The resolution of fibrinous exudates, with exhibition of specimens.

Ottenberg, Reuben [with **William J. Gies.**]

256. On the fate of elastose after its subcutaneous or intraperitoneal injection: a preliminary inquiry into the origin and nature of Bence Jones's protein.

Pearce, Richard M. [with **Holmes C. Jackson.**]

192. Experimental liver necrosis: 1. Hexon bases.

Pike, F. H. [with **G. N. Stewart.**]

199. The automatism of the respiratory center.

Rankin, Allan C. (by invitation) [with **A. A. Martin.**]

198. Observations on the effects of fasting upon the opsonic power of the blood to staphylococcus aureus.

Robertson, T. Brailsford

237. On the dissociation in solutions of the neutral caseinates of sodium and ammonium.

Rous, F. Peyton

234. The effects of struggle on the content of white cells in the lymph. [Communicated by **Aldred S. Warthin.**]

Rutherford, Thomas A. [with **Philip B. Hawk.**]

196. Comparative chemical composition of the hair of different races.

Salant, William [with **F. C. Hinkel.**]

180. The influence of alcohol on the composition of urine.

Sherman, H. C.

161. Experiments upon the total metabolism of iron and calcium in man.

Snow, C.

233. An experimental control of Fischer's attraxin theory. [Communicated by **Aldred S. Warthin.**]

Stewart, G. N. [with **F. H. Pike.**]

199. The automatism of the respiratory center.

Stiles, Percy G.

216. On magnesium and contractile tissues.

Stookey, Lyman B.

184. The effect of salicylic acid upon autolysis.

Sweet, J. E. [with **P. A. Levene.**]

157. Nuclein metabolism in a dog with an Eck fistula.

Taylor, Alonzo Englebert

185. On the synthesis of protein through the action of trypsin.

Teague, Oscar [with **Cyrus W. Field.**]

156. The action of the electric current on toxin and antitoxin.

Torrey, John C.

214. Agglutinins and precipitins in anti-gonococcic serum.

Tyzzer, E. E.

200. A series of spontaneous tumors in mice.

Underhill, Frank P.

242. The presence of allantoin in the urine of the dog during starvation.

Vaughan, Victor C.

240. Proteid poisons.

Warthin, Aldred S.

232. Experimental ligation of splenic and portal veins, with the aim of producing a form of splenic anemia.

233. [For **C. Snow.**] An experimental control of Fischer's attraxin theory.

234. [For **F. Peyton Rous.**] The effects of struggle on the content of white cells in the lymph.

Weil, Richard [by invitation.]

166. The hemolytic effects of organ and tumor extracts.

Wolf, C. G. L.

144. [With **R. A. Hatcher.**] The formation of glycogen from sugars by muscle, with a demonstration of a perfusion apparatus.

204. [With **W. McKim Marriott.**] The determination of ammonia and urea in blood.

Woolley, Paul G. [by invitation.]

228. The bacteriotherapy of leprosy.

Yatsu, Naohidé

160. An experiment on the localization problem in the egg of Cerebratulus.

Yerkes, Robert M.

147. The senses and intelligence of the Chinese dancing mouse.

CLASSIFIED LIST OF CONTRIBUTING LABORATORIES.

(Communications in Volume IV.)

Albany Medical College : *Physiological Chemistry*—192.[1]

Carnegie Institution's Station for Experimental Evolution—244.

Chicago University : *Biochemistry and Pharmacology* — 197 ; *Physiology* — 199, 236.

Columbia University : *Chemistry* — 161 ; *Biological Chemistry* — 150, 155, 159, 180, 243, 254, 255, 256 ; *Pathology* — 178 ; *Physiology* — 162, 163, 164, 165, 179, 182, 183, 202, 203, 212, 213 ; *Zoology* — 160, 181, 187, 254.

Cooper Medical College : *Pathology* — 238, 239.

Cornell University Medical College : *Chemistry* — 144, 204 ; *Experimental Pathology*, Loomis Laboratory — 145, 188, 214, 226 ; *Huntington Fund for Cancer Research* of the General Memorial Hospital, Loomis Laboratory — 166 ; *Pathology*—223 ; *Pharmacology* — 144.

Department of Health, of New York City : *Research* Laboratory — 156, 158, 246, 247.

Harvard University : *Biological Chemistry* — 201 ; *Caroline Brewer Croft Cancer Commission* — 200 ; *Physiology* — 148 ; *Psychology* — 147.

Herter's private laboratory — 230.

Johns Hopkins University : *Anatomy* — 241 ; *Physiology* — 222.

Massachusetts Institute of Technology — 216.

McGill University : *Pathology* — 198.

McLean Hospital : *Chemistry* — 215.

New York University : *Chemistry* — 225 ; *Physiology* — 224.

Rockefeller Institute — 150, 151, 152, 153, 154, 157, 167, 170, 171, 172, 173, 174, 176, 177, 186, 205, 206, 209, 210, 211, 217, 218, 219, 220, 221, 227, 229, 235, 248, 250, 251, 252, 253.

Siam Serum Laboratory (Phrapatoom) — 228.

University of California : *Pathology* — 185 ; *Physiology* — 195, 237.

University of Maryland : *Physiology* —249.

University of Michigan : *Hygiene* — 175, 240 ; *Pathology* — 232, 233, 234 ; *Physiology* — 146.

University of Pennsylvania : *Experimental Pathology* — 207, 208 ; *Physiological Chemistry* — 196 ; *Zoology* — 169.

University of Southern California : *Physiology* — 184.

University of Toronto : *Physiology* — 193.

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[1] The numerals correspond with those in parenthesis above the titles of the abstracts (pages 1–162).

University of West Virginia: *Bacteriology* — 231.
University of Wisconsin: *Anatomy* — 245.
Wesleyan University: *Chemistry* — 255.
Western Reserve University: *Physiology* — 168, 191; *Surgical Pathology* — 149, 189, 190.
Yale University: *Physiological Chemistry* — 194, 242.

EXECUTIVE PROCEEDINGS.

QUOTATIONS FROM THE MINUTES.

Eighteenth meeting.

Cornell University Medical College, New York City. October 17, 1906. President Flexner in the chair.

Members present: Atkinson, Auer, Beebe, Buxton, Crile, Dunham, Elser, Emerson, Ewing, Field, Flexner, Flournoy, Foster, Gibson, Gies, Hatcher, Lee, Levene, Levin, Loeb (L.), Lusk, Mandel (A. R.), Meltzer, Meyer, Murlin, Norris, Park, Richards, Salant, Schwyzer, Shaffer, Torrey, Wallace, Wolf, Wood, Yerkes.

Prompt publication of the proceedings. The Secretary suggested that, in order to facilitate prompt issuance of abstracts of the communications, the Proceedings, beginning with Vol. IV, be distributed in sections, a section to be published as soon as possible after each meeting and to consist of the abstracts relating to that particular session. This suggestion was unanimously adopted.

Nineteenth meeting.

Schermerhorn Hall, Columbia University. December 19, 1906. President Flexner in the chair.

Members present: Auer, Beebe, Burton-Opitz, Calkins, Davenport, Emerson, Ewing, Flexner, Foster, Gies, Hatcher, Lusk, Mandel (A. R.), Meltzer, Meyer, Morgan, Noguchi, Norris, Sherman, Shaffer, Torrey, Wolf, Yatsu.

Members elected: Alexis Carrel, Winfield S. Hall, William Ophüls, H. Gideon Wells.

Twentieth meeting.

[Fourth annual business meeting.]

Rockefeller Institute for Medical Research. February 20, 1907. President Flexner in the chair.

Members present: Adler, Burton-Opitz, Calkins, Carrel, Conklin, Emerson, Ewing, Field, Flexner, Foster, Gibson, Gies,

Lee, Levene, Levin, Mandel (J. A.), Meltzer, Meyer, Murlin, Noguchi, Opie, Salant, Wolf, Yatsu.

Member elected: C. Ward Crampton.

Officers elected: President, Flexner; Vice-president, Morgan; Treasurer, Calkins; Secretary, Gies.

Treasurer's report. — The main items of the Treasurer's report were the following:

Receipts	$290.15
Expenditures, including the deficit of 1906 ($37.37)	261.97
Balance in the treasury	$ 28.18

Twenty first meeting.

College of Physicians and Surgeons, Columbia University. March 20, 1907. President Flexner in the chair.

Members present: Adler, Beebe, Burton-Opitz, Carrel, Crampton, Crile, Emerson, Ewing, Field, Flexner, Gibson, Gies, Hatcher, Lee, Levene, Levin, Lusk, Mandel (J. A.), Meltzer, Murlin, Noguchi, Opie, Richards, Schwyzer, Shaffer, Torrey, Tyzzer, Wadsworth, Wallace, Wolf.

Twenty second meeting.

Rockefeller Institute for Medical Research. April 17, 1907. President Flexner in the chair.

Members present: Auer, Beebe, Burton-Opitz, Calkins, Carrel, Emerson, Ewing, Field, Flexner, Gibson, Gies, Hatcher, Kast, Levene, Loeb (L.), Meltzer, Morgan, Noguchi, Richards, Salant, Shaffer, Teague, Torrey, Wadsworth, Wallace, Wolf, Wood.

Members elected: Robert R. Bensley, William T. Councilman, Ludwig Kast, Waldemar Koch, Ward J. MacNeal, F. P. Mall, T. Brailsford Robertson, Oscar Teague, Richard Weil.

Twenty third meeting.

New York University and Bellevue Hospital Medical College. May 22, 1907. President Flexner in the chair.

Members present: Atkinson, Beebe, Brooks, Calkins, Carrel, Emerson, Ewing, Field, Flexner, Gibson, Gies, Lillie, Lusk, Meyer, Murlin, Salant, Shaffer, Teague, Wadsworth, Weil, Wolf, Yatsu.

Amendments of the Constitution. — The following amendments of Article VI of the Constitution, which were proposed by the Treasurer and which had been duly presented at the twenty second meeting, were adopted by unanimous vote of the members present:

XIII.[1] New section — 2. *Privileges of membership begin with payment of dues.* Candidates for membership, if elected, shall not be entitled to any of the privileges of membership before they pay the dues for the fiscal year in which their election occurs.

XIV. Substitute for former section 2: Section 3. *Penalty for non-payment of dues.* Members in arrears for dues for a period of three consecutive years shall thereupon forfeit their membership, but may be reinstated by the Council.

Twenty fourth meeting.

Carnegie Institution's Station for Experimental Evolution, Cold Spring Harbor, Long Island, New York. June 22, 1907. President Flexner in the chair.

Members present: Atkinson, Beebe, Carrel, Davenport, Donaldson, Ewing, Field, Flexner, Gibson, Gies, Hatcher, Lusk, Meltzer, Meyer, Shaffer, Wallace, Wadsworth.

Members elected: C. H. Bunting, Rufus I. Cole, Charles W. Duval, William W. Ford, Frederick P. Gay, Isaac F. Harris, James W. Jobling, Oskar Klotz, Paul A. Lewis, Thomas B. Osborne, H. T. Ricketts.

[1] Amendments X, XI and XII were given on page 89 of Volume III of the Proceedings. Amendment X is included in recommendation 5 of the "special report of the council." The numerals before the amendments at the bottom of page 89 of Volume III of the Proceedings should have been XI and XII respectively.

LIST OF OFFICERS.

Fourth year: February, 1906–February, 1907.

President..... Simon Flexner.
Vice-president..... Edward K. Dunham.
Treasurer..... Gary N. Calkins.
Secretary..... William J. Gies.
Council — S. J. Meltzer, Edmund B. Wilson, Simon Flexner, Edward K. Dunham, Gary N. Calkins and William J. Gies.

Fifth year: February, 1907–February, 1908.

President..... Simon Flexner.
Vice-president..... Thomas H. Morgan.
Treasurer..... Gary N. Calkins.
Secretary..... William J. Gies.
Council — S. J. Meltzer, Edmund B. Wilson, Simon Flexner, Thomas H. Morgan, Gary N. Calkins and William J. Gies.

REGISTER OF NAMES AND ADDRESSES OF THE MEMBERS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE.

ABBOTT, ALEXANDER C. .....University of Pennsylvania.
ABEL, JOHN J. .....Johns Hopkins University.
ADAMI, J. GEORGE.....McGill University, Montreal.
ADLER, ISAAC.....New York Polyclinic Medical School.
ALSBERG, CARL L.....Harvard University.
ATKINSON, JAMES P..... .....Department of Health, New York City.
AUER, JOHN.....Rockefeller Institute for Medical Research.

BARDEEN, CHARLES R.....Wisconsin University.
BEEBE, S. P..... .....Cornell University Medical College.
BENEDICT, FRANCIS G.....Wesleyan University.
BENSLEY, ROBERT R.....Chicago University.
BRINCKERHOFF, WALTER R.....U. S. Public Health and Marine Hospital Service, Honolulu.
BROOKS, HARLOW.....New York University.
BUNTING, C. H.....University of Virginia.
BURTON-OPITZ, RUSSELL.....Columbia University.
BUXTON, B. H.....Cornell University Medical College.

CALKINS, GARY N..... .....Columbia University.
CANNON, WALTER B.....Harvard University.
CARLSON, A. J.....Chicago University.
CARREL, ALEXIS.....Rockefeller Institute for Medical Research.
CHITTENDEN, R. H..... .....Yale University.
CLOWES, G. H. A.....Buffalo University.
COLE, RUFUS I.....Johns Hopkins University.
CONKLIN, EDWIN G.....University of Pennsylvania.
COUNCILMAN, WILLIAM T.....Harvard University.
CRAMPTON, C. WARD.....Department of Education, New York City.
CRAMPTON, HENRY E.....Columbia University.
CRILE, GEORGE W.....Western Reserve University, Cleveland, O.
CUNNINGHAM, RICHARD H.....Columbia University.
CUSHING, HARVEY W.....Johns Hopkins University.
CUSHNY, ARTHUR R.....University College, London.

DAVENPORT, CHARLES B.....Carnegie Institution's Station for Experimental Evolution, Cold Spring Harbor, Long Island, N. Y.

DAWSON, PERCY M.....Johns Hopkins University.
DONALDSON, H. H.....Wistar Institute of Anatomy, Philadelphia.
DUNHAM, EDWARD K.....New York University.
DUVAL, CHARLES W.....McGill University, Montreal.

EDSALL, DAVID L.....University of Pennsylvania.
ELSER, W. J.....Cornell University Medical College.
EMERSON, HAVEN.....Columbia University.
ERLANGER, JOSEPH.....University of Wisconsin.
EWING, JAMES.....Cornell University Medical College.

FIELD, CYRUS W.....Department of Health, New York City.
FLEXNER, SIMON.....Rockefeller Institute for Medical Research.
FLOURNOY, THOMAS.....Bellevue Hospital, New York City.
FOLIN, OTTO.....Harvard University.
FORD, WILLIAM W.....Johns Hopkins University.
FOSTER, NELLIS B.....Columbia University.

GAY, FREDERICK P.....Harvard University.
GIBSON, ROBERT B.....University of Missouri.
GIES, WILLIAM J.....Columbia University.

HARRIS, ISAAC F.....19 West 42d Street, New York City.
HARRISON, ROSS G.....Johns Hopkins University.
HATCHER, ROBERT A.....Cornell University Medical College.
HAWK, PHILIP B.....University of Illinois.
HEKTOEN, LUDVIG.....Chicago University.
HENDERSON, YANDELL.....Yale University.
HERTER, CHRISTIAN A.....Columbia University.
HISS, PHILIP H.....Columbia University.
HOWELL, WILLIAM H.....Johns Hopkins University.
HUBER, CARL G.....University of Michigan.
HUNT, REID.....U. S. Public Health and Marine-Hospital Service, Hygienic Laboratory, Washington, D. C.

JACKSON, HOLMES C.....Albany Medical College.
JOBLING, JAMES W.....Rockefeller Institute for Medical Research.
JONES, WALTER.....Johns Hopkins University.
JORDAN, EDWIN O.....Chicago University.

KAST, LUDWIG.....Rockefeller Institute for Medical Research.
KASTLE, JOSEPH H.....U. S. Public Health and Marine-Hospital Service, Hygienic Laboratory, Washington, D. C.
KLOTZ, OSKAR.....McGill University, Montreal.
KOCH, WALDEMAR.....Chicago University.

LEE, FREDERIC S.....Columbia University.
LEVENE, P. A.....Rockefeller Institute for Medical Research.

LEVIN, ISAAC.....Sydenham Hospital, New York City.
LEWIS, PAUL A.....Massachusetts Department of Health, Boston.
LILLIE, RALPH S.....Johns Hopkins University.
LOEB, JACQUES.....University of California.
LOEB, LEO.....University of Pennsylvania.
LOEVENHART, ARTHUR S.....Johns Hopkins University.
LOMBARD, WARREN P.....University of Michigan.
LUSK, GRAHAM.....New York University.

MACALLUM, A. B.....University of Toronto.
MACCALLUM, W. G.....Johns Hopkins University.
MACDOUGAL, D. T.....Carnegie Institution, Washington, D. C.
MACLEOD, J. J. R.....Western Reserve University, Cleveland, O.
MACNEAL, WARD J.....University of Illinois.
MALL, F. P.....Johns Hopkins University.
MANDEL, ARTHUR R.....New York University.
MANDEL, JOHN A.....New York University.
MATHEWS, ALBERT P.....Chicago University.
MELTZER, S. J.....Rockefeller Institute for Medical Research.
MENDEL, LAFAYETTE B.....Yale University.
MEYER, GUSTAVE M.....Columbia University.
MORGAN, THOMAS H.....Columbia University.
MURLIN, JOHN R.....New York University.

NOGUCHI, HIDEYO.....Rockefeller Institute for Medical Research.
NORRIS, CHARLES.....Bellevue Hospital, New York City.
NOVY, FREDERICK G.....University of Michigan.

OERTEL, HORST.....Columbia University.
OPHÜLS, WILLIAM.....Cooper Medical College, San Francisco.
OPIE, EUGENE L.....Rockefeller Institute for Medical Research.
OSBORNE, THOMAS B.....Connecticut Agricultural Experiment Station, New Haven.

PARK, WILLIAM H.....New York University.
PARKER, G. H.....Harvard University.
PEARCE, RICHARD M.....Albany Medical College.
PFAFF, FRANZ.....Harvard University.
PORTER, W. T.....Harvard University.
PRATT, JOSEPH H.....Harvard University.

RICHARDS, ALFRED N.....Columbia University.
RICKETTS, H. T.....Chicago University.
ROBERTSON, T. BRAILSFORD.....University of California.

SALANT, WILLIAM.....University of Alabama.
SCHWYZER, FRITZ.....St. Francis Hospital, New York City.

SHAFFER, PHILIP A.....Cornell University Medical College.
SHERMAN, HENRY C.....Columbia University.
SMITH, THEOBALD.....Harvard University.
SOLLMANN, TORALD.....Western Reserve University, Cleveland, O.
STEWART, G. N.....Chicago University.
STILES, PERCY G.....Massachusetts Institute of Technology.
STOOKEY, LYMAN B.....University of Southern California, Los Angeles.
SWEET, J. EDWIN.....University of Pennsylvania.
SYMMERS, DOUGLAS.....New York City Hospital.

TAYLOR, ALONZO E.....University of California.
TEAGUE, OSCAR.....Cornell University Medical College.
TERRY, B. T.....Rockefeller Institute for Medical Research.
TORREY, JOHN C.....Cornell University Medical College.
TYZZER, E. E.....Harvard University.

UNDERHILL, FRANK P.....Yale University.

VAUGHAN, VICTOR C.....University of Michigan.

WADSWORTH, AUGUSTUS B.....Columbia University.
WALLACE, GEORGE B.....New York University.
WARTHIN, ALDRED S.....University of Michigan.
WEIL, RICHARD.....Cornell University Medical College.
WELCH, WILLIAM H.....Johns Hopkins University.
WELLS, H. GIDEON.....Chicago University.
WILLIAMS, HERBERT U.....Buffalo University.
WILSON, EDMUND B.....Columbia University.
WOLF, CHARLES G. L.....Cornell University Medical College.
WOOD, FRANCIS C.....Columbia University.
WOODRUFF, L. L.....Williams College, Williamstown, Mass.

YATSU, NAOHIDÉ.....Columbia University.
YERKES, ROBERT M.....Harvard University.

Total number of members at the close of the academic year, 1906–'07: **140**.

CLASSIFIED LIST OF MEMBERS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE.

Resident (Greater New York).

Bellevue Hospital.—Thomas Flournoy, Charles Norris.

Columbia University.—Russell Burton-Opitz, Gary N. Calkins, Henry E. Crampton, Richard H. Cunningham, Haven Emerson, Nellis B. Foster, William J. Gies, Christian A. Herter, Philip H. Hiss, Frederic S. Lee, Gustave M. Meyer, T. H. Morgan, Horst Oertel, Alfred N. Richards, H. C. Sherman, Augustus B. Wadsworth, Edmund B. Wilson, Francis C. Wood, Naohidé Yatsu.

Cornell University Medical College.—S. P. Beebe, B. H. Buxton, W. J. Elser, James Ewing, R. A. Hatcher, Philip A. Shaffer, Oscar Teague, John C. Torrey, Richard Weil, C. G. L. Wolf.

New York Department of Education.—C. Ward Crampton.

New York Department of Health.—James P. Atkinson, Cyrus W. Field.

New York Hospital.—Douglas Symmers.

New York Polyclinic Medical School.—Isaac Adler.

New York University.—Harlow Brooks, Edward K. Dunham, Graham Lusk, Arthur R. Mandel, John A. Mandel, J. R. Murlin, William H. Park, George B. Wallace.

Rockefeller Institute for Medical Research.—John Auer, Alexis Carrel, Simon Flexner, J. W. Jobling, Ludwig Kast, P. A. Levene, S. J. Meltzer, Hideyo Noguchi, E. L. Opie, B. T. Terry.

St. Francis Hospital.—Fritz Schwyzer.

Sydenham Hospital.—Isaac Levin.

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19 W. 42d Street.—Isaac F. Harris.

Non-Resident.

Albany Medical College.—Holmes C. Jackson, Richard M. Pearce.

Buffalo University.—G. H. A. Clowes, Herbert U. Williams.

Carnegie Institution of Washington.—D. T. MacDougal.

Carnegie Institution's Station for Experimental Evolution (Cold Spring Harbor, N. Y.).—Charles B. Davenport.

Chicago University.—R. R. Bensley, A. J. Carlson, Ludvig Hektoen, E. O. Jordan, Waldemar Koch, Albert P. Mathews, H. T. Ricketts, G. N. Stewart, H. Gideon Wells.

Connecticut Agricultural Experiment Station (New Haven).—Thomas B. Osborne.

Cooper Medical College (San Francisco).—William Ophüls.

Harvard University.—Carl L. Alsberg, Walter B. Cannon, W. T. Councilman, Otto Folin, Frederick P. Gay, G. H. Parker, Franz Pfaff, W. T. Porter, Joseph H. Pratt, Theobald Smith, E. E. Tyzzer, Robert M. Yerkes.

Johns Hopkins University.—John J. Abel, Rufus I. Cole, Harvey W. Cushing, Percy M. Dawson, W. W. Ford, Ross G. Harrison, William H. Howell, Walter Jones, Ralph S. Lillie, A. S. Loevenhart, W. G. MacCallum, F. P. Mall, William H. Welch.

Massachusetts Department of Health (Boston).—Paul A. Lewis.

Massachusetts Institute of Technology.—Percy G. Stiles.

McGill University (Montreal).—J. George Adami, Charles W. Duval, Oskar Klotz.

U. S. Public Health and Marine Hospital Service.—Walter R. Brinckerhoff (Honolulu), Reid Hunt (Washington), J. H. Kastle (Washington).

University College (London).—Arthur R. Cushny.

University of Alabama.—William Salant.

University of California.—Jacques Loeb, T. Brailsford Robertson, Alonzo E. Taylor.

University of Illinois.—Philip B. Hawk, Ward J. MacNeal.

University of Michigan.—Carl G. Huber, Warren P. Lombard, Frederick G. Novy, Victor C. Vaughan, Aldred S. Warthin.

University of Missouri.—Robert B. Gibson.

University of Pennsylvania.—Alexander C. Abbott, E. G. Conklin, David L. Edsall, Leo Loeb, J. Edwin Sweet.

University of Southern California (Los Angeles).—Lyman B. Stookey.

University of Toronto.—A. B. Macallum.

University of Virginia.—C. H. Bunting.

University of Wisconsin.—Charles R. Bardeen, Joseph Erlanger.

Wesleyan University (Middletown, Conn.).—Francis G. Benedict.

Western Reserve University (Cleveland).—George W. Crile, J. J. R. Macleod, Torald Sollmann.

Williams College (Williamstown, Mass.).—L. L. Woodruff.

Wistar Institute of Anatomy (Philadelphia).—H. H. Donaldson.

Yale University.—R. H. Chittenden, Yandell Henderson, L. B. Mendel, Frank P. Underhill.

CONSTITUTION AND BY-LAWS.

CONSTITUTION.

[As adopted February 25, 1903, and amended April 20, 1904, May 24, 1905, February 21, 1906, April 18, 1906 and May 22, 1907.][1]

Article I. Name.

The name of this organization shall be the Society for Experimental Biology and Medicine.

Article II. Object.

The object of this Society shall be the cultivation of the experimental method of investigation in the sciences of animal biology and medicine.

Article III. Membership.

Section 1. *Eligibility.* — Any person who has accomplished a meritorious original investigation in biology or medicine by the experimental method shall be eligible to membership.

Section 2. *Classification.* — The term "resident members" shall refer, in this constitution, to those members whose experimental work shall be done within the limits of "Greater New York"; "non-resident members," to those whose scientific work shall be done outside of "Greater New York."

Section 3. *Obligations.* — A. Every member shall be expected to conduct an experimental investigation, and give public notice of it, at least once in two years.

B. *Resident* members shall be required either to attend, every two years, at least three meetings of the Society, or to present in person, at least once every two years, a report of their experimental researches.

C. Each *non-resident* member shall be required to present in person, at least once every two years, a communication containing the results of an experimental investigation, or to send to the President within that time, such a communication for presentation at a regular meeting of the Society.

[1] The amendments adopted May 22, 1907 are indicated by heavy-faced letters.

D. Non-compliance with any of these requirements carries with it forfeiture of membership, unless an acceptable explanation is offered to the Council.

E. Any member of this Society who may consent to the use of his name in any way that would aid in increasing the sale of any patent medicine, proprietary food preparation, or any similar product known to be of doubtful value, shall forfeit his membership.

SECTION 4. *Nomination and Election.* — A. Each candidate for membership must be nominated by three members.

B. After their eligibility has been determined by the Council, nominees may be voted for at any meeting succeeding that at which their names were presented.

C. A three fourths vote of the ballots cast shall elect.

SECTION 5. *Expulsion.* — Any member may be expelled by a three fourths vote of the total membership.

ARTICLE IV. MEETINGS.

SECTION 1. *Time.* —The Society shall hold regular meetings at least once every two months during the academic year.

SECTION 2. *Annual Business.* —The first regular meeting of each calendar year shall be an annual business meeting.

SECTION 3. *Program.* — The programs of the meetings shall consist of (A) brief presentations, in elementary form, of the essential points of experimental investigations, preferably demonstrations of actual experiments; and (B) of brief reports of important facts recently discovered in the sciences of biology and medicine or allied natural sciences.

ARTICLE V. OFFICIALS.

SECTION 1. *Officers.* — The officers shall be a President, a Vice-president, a Secretary and a Treasurer.

SECTION 2. *Council.* — The officers shall constitute the Council of the Society. Ex-Presidents of the Society shall be ex-officio permanent members of the Council.

SECTION 3. *Nomination and Election.* — A. Nominations of officers shall be made in the regular session immediately preceding the annual business meeting.

B. Election of officers shall be by ballot at the annual business meeting.

C. A plurality of the votes cast shall elect.

SECTION 4. *Term of Office.* — The term of office shall be one calendar year.

SECTION 5. *Duties.* — A. The duties of the officers shall be such as usually devolve on them individually, and also collectively, as an executive committee.

B. The Council shall promptly investigate and report its findings on the eligibility of candidates for membership and on the desirability of each candidate's election.

ARTICLE VI. FINANCIAL.

SECTION 1. *Dues.* — The annual dues shall be Two Dollars ($2.00), unless otherwise determined by the Council.

Section 2. Privileges of membership begin with payment of dues. Candidates for membership, if elected, shall not be entitled to any of the privileges of membership before they pay the dues for the fiscal year in which their election occurs.

Section 3. Penalty for non-payment of dues. Members in arrears for dues for a period of three consecutive years shall thereupon forfeit their membership, but may be reinstated by the Council.

ARTICLE VII. QUORUM.

Twenty members shall constitute a quorum for the transaction of business.

ARTICLE VIII. BY-LAWS.

By-laws may be adopted at any meeting by a majority vote.

ARTICLE IX. AMENDMENTS.

SECTION 1. Proposed amendments of the constitution must be endorsed by at least three members, at a regular meeting, and may be voted on at a succeeding meeting.

SECTION 2. It shall be the duty of the Secretary to give all members due notice of intended amendments.

SECTION 3. A two thirds vote of the total membership, or a unanimous vote of the members present, shall be required for the adoption of an amendment.

BY-LAWS.

[Adopted February 25, 1903, and amended May 24, 1905 and February 21, 1906.]

I. *Meetings.* — A. The regular meetings shall be held on the third Wednesdays of October, December, February, April and May.

B. Special meetings may be called by the Council.

C. The meetings shall be opened at 8:15 p. m., and shall be closed at 10:30 p. m.

D. When possible the meetings shall take place in suitable laboratories.

II. *Regulation of Reports and Discussions.* — A. The time allowed for making individual communications, except demonstrations of experiments, shall be restricted to ten minutes.

B. Precedence shall be given, on each program, to communications which have not been presented before any other body and which have to do with investigations essentially experimental in character.

C. Not more than five minutes shall be allowed to a member for the discussion of any communication.

III. *Order of Procedure to be followed at the regular meetings:*

A. Call to order.

B. Reading of minutes.

C. Report of council.

D. Scientific program.

E. Executive program:

a. Reports of committees.

b. Unfinished business.

c. Election of members.

d. Nominations for membership.

e. New business.

F. Adjournment.

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Edwin O. Jordan

PROCEEDINGS

OF THE

SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE

EIGHTEENTH MEETING

CORNELL UNIVERSITY MEDICAL COLLEGE

NEW YORK CITY

OCTOBER 17, 1906

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No. 1

NEW YORK

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13. The action of the electric current on toxin and antitoxin. By **Cyrus W. Field** and **Oscar Teague.**

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NEW YORK CITY

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TWENTIETH MEETING

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Alexis Carrel, Winfield S. Hall, William Ophüls, H. Gideon Wells.

Dates of the next three regular meetings.

February 20, 1907 (fourth annual business meeting).

April 17, 1907.

May 22, 1907.

Date of the next special meeting.

March 20, 1907.

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Members present at the eighteenth meeting.

Atkinson, Auer, Beebe, Buxton, Crile, Dunham, Elser, Emerson, Ewing, Field, Flexner, Flournoy, Foster, Gibson, Gies, Hatcher, Lee, Levene, Levin, Loeb (L.), Lusk, Mandel (A. R.), Meltzer, Meyer, Murlin, Norris, Park, Richards, Salant, Schwyzer, Shaffer, Torrey, Wallace, Wolf, Wood, Yerkes.

Dates of the next two meetings :

December 19, 1906.

February 20, 1907 (fourth annual business meeting).

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PROCEEDINGS

OF THE

SOCIETY FOR

EXPERIMENTAL BIOLOGY AND MEDICINE

TWENTY FIRST MEETING

COLLEGE OF PHYSICIANS AND SURGEONS

COLUMBIA UNIVERSITY

NEW YORK CITY

MARCH 20, 1907

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No. 4

NEW YORK

APRIL 15, 1907

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SOCIETY FOR

EXPERIMENTAL BIOLOGY AND MEDICINE

TWENTY SECOND MEETING

ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

NEW YORK CITY

APRIL 17, 1907

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NEW YORK

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77 (220). On the diuretic action of thymin. By **P. A. Levene.**

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OF THE

SOCIETY FOR

EXPERIMENTAL BIOLOGY AND MEDICINE

TWENTY THIRD MEETING

NEW YORK UNIVERSITY

AND

BELLEVUE HOSPITAL MEDICAL COLLEGE

NEW YORK CITY

MAY 22, 1907

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No. 6

NEW YORK

JUNE 15, 1907

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PROCEEDINGS

OF THE

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TWENTY FOURTH MEETING

CARNEGIE INSTITUTION'S
STATION FOR EXPERIMENTAL EVOLUTION
COLD SPRING HARBOR
LONG ISLAND, N. Y.

JUNE 22, 1907

VOLUME IV

No. 7

(WITH TITLE PAGE, INDEX, ETC., FOR VOLUME IV.)

NEW YORK

AUGUST 1, 1907

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Dates of the next two regular meetings:

October 16, 1907.
December 18, 1907.

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Date of the first fall meeting:

October 16, 1907.

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